Synthesis of precursors en route to the basic skeleton of the anti-tumor drug Taxol

Dissertation

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Gutachter: Prof. M. Demuth und Prof. R. Sustmann

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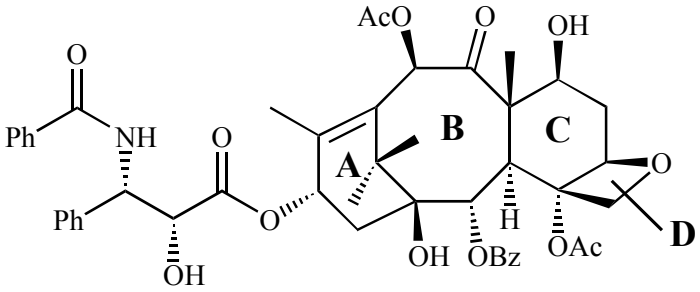
To my Parents

CONTENTS

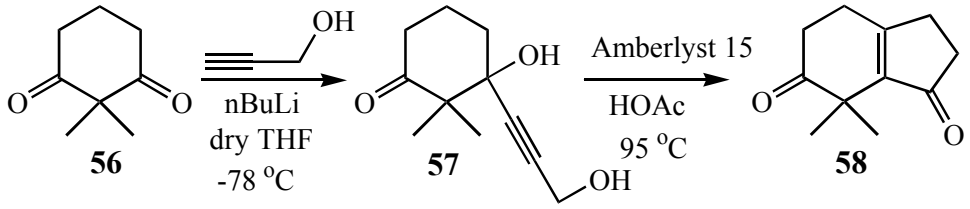
1 Abstract

In this work, a new and efficient synthesis of 9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione, which is a potential precursor of the ABC ring skeleton of the anti-tumor drug taxol (**1**), has been synthesized by using a photochemical oxa-di-π-methane rearrangement as a key reaction.

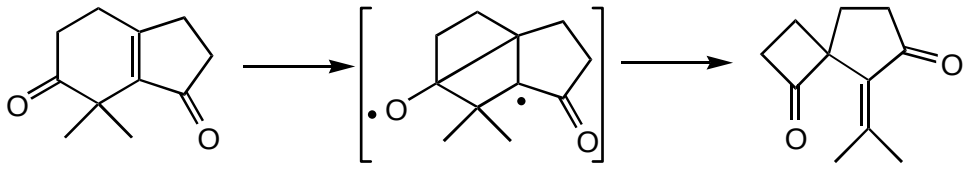
Taxol (**1**):



The synthesis starts with the addition of dilithated propargyl alcohol to 2,2-dimethylcyclohexa-1,6-dione (**56**). The product **57** was then subjected to a *Nazarov*-type cyclization in order to obtain the β,γ-unsaturated endione **58**. Treatment with CH_3OH/H_2SO_4, $HOAc/H_2SO_4$ and P_2O_5/CH_3SO_3H resulted in the decomposition of the starting compound. Reaction of **57** with amberlyst 15 gave, however, the expected compound **58**.

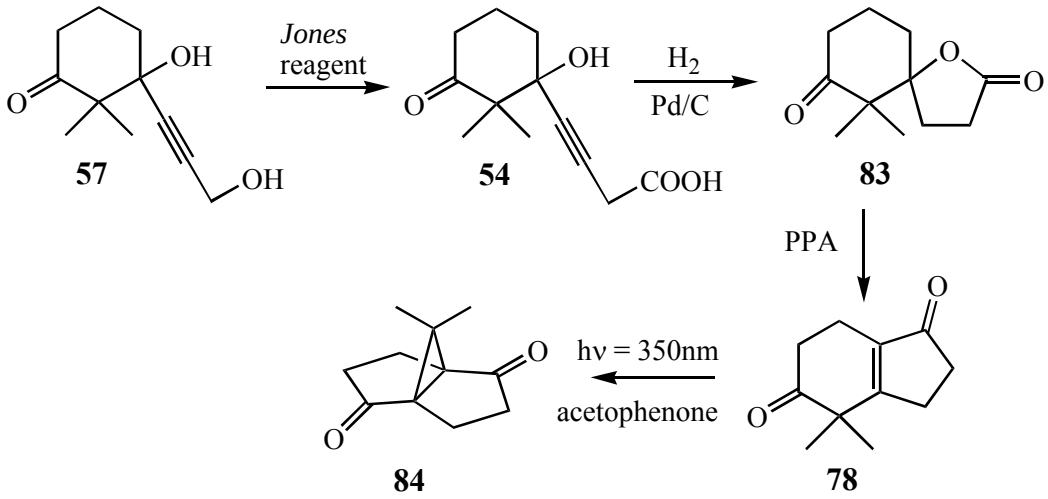


Oxa-di-π-methane rearrangements, which are analogs of the di-π-methane rearrangement, are widely applied for the synthesis of natural products. Irradiation of **58** in the presence of acetophenone as sensitizer with the 350-nm light (*Rayonet* reactor) gave the unexpected product **77**. Failure of this transformation has been explained by the stabilization of one of the possible intermediate radicals **76**. The generated intermediate radical seems to be 1,3-acyl shift product which was stabilized by the neighboring carbonyl groups.



58 **76** **77**

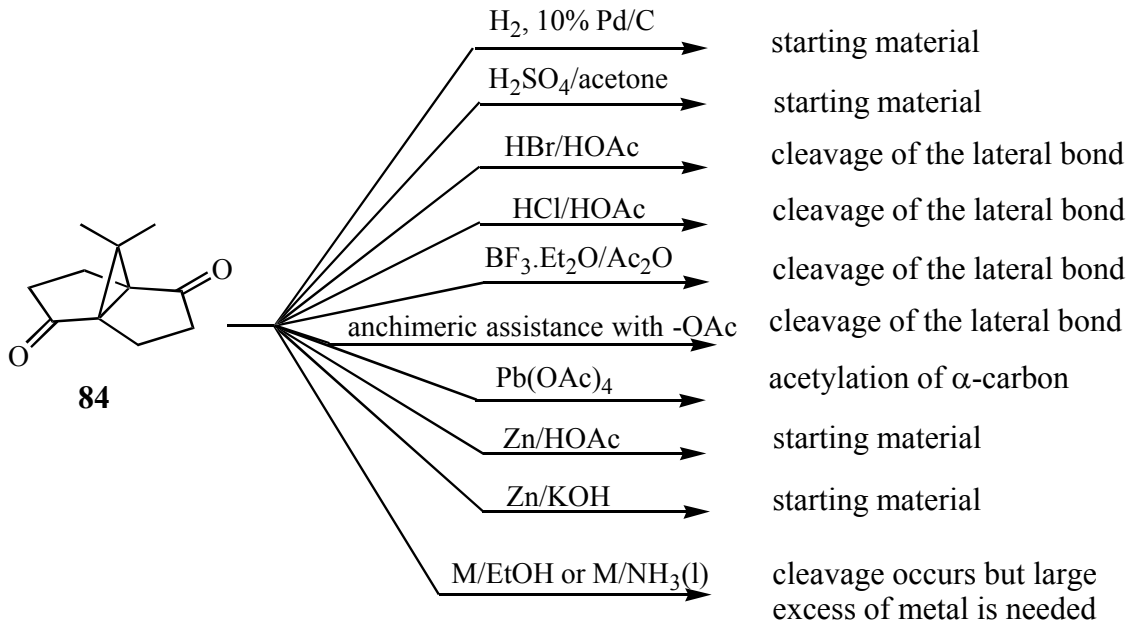
Efforts were then directed to the synthesis of another β,γ-enone so that the oxa-di-π-methane rearrangement would not have the intermediate like **76**. For this reason, **57** was oxidized with *Jones* reagent and then hydrogenated on 10% Pd/charcoal. When the obtained cyclic lactone **83** was treated with polyphosphoric acid (PPA) the target β,γ-endione **78** was obtained in 60% yield. The oxa-di-π-methane rearrangement of **78** to **84** was achieved by irradiating at 350-nm light (*Rayonet* reactor) and acetophenone was used as the sensitizer with a yield of 87%.



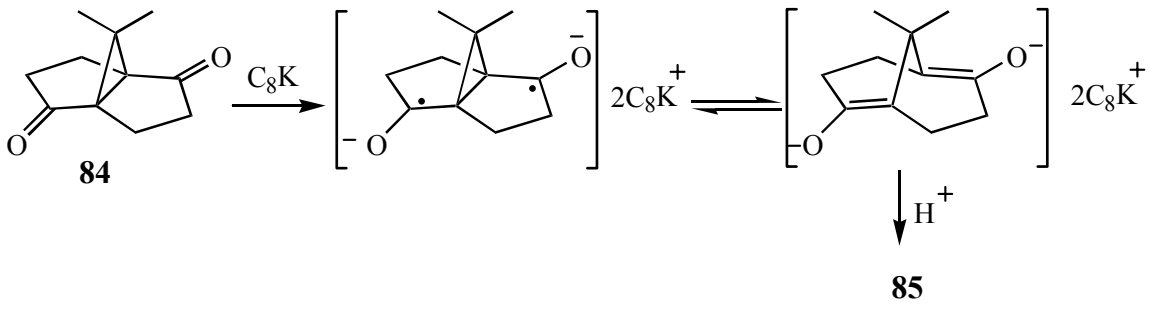
57 **54** **83** **84** **78**

The next important step of this work was the cleavage of the central cyclopropane bond of **84**. Attempts of cleavage included hydrogenation, H_2SO_4 in acetone, HBr in HOAc, HCl in HOAc, $BF_3 \cdot Et_2O$ in acetic anhydride treatment. Furthermore, neighboring group participation to facilitate the cleavage by push-pull mechanisms, oxidative opening with $Pb(OAc)_4$ and dissolving metal reduction like *Birch* and *Bouveault-Blanc* reductions have also been tried. Although these methods work for other compounds, they were not successful in cleaving the central bond of **84**; either the starting material was recovered or

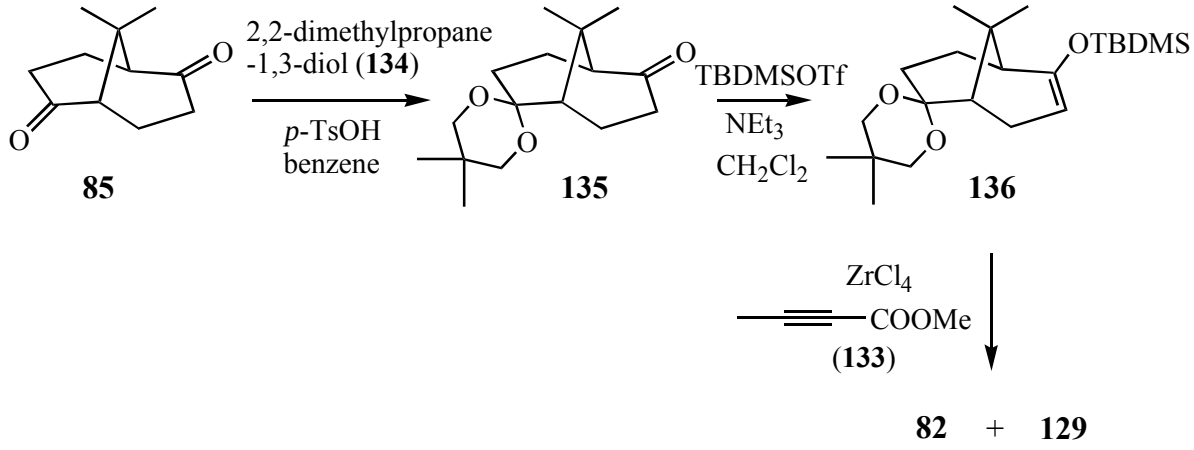
lateral bond cleaved in the cyclopropane occured. Reasons are, depent on the methodapplied, either the lack of sufficient orbital interaction between the carbonyls and the cyclopropane bond which is intended to be cleaved or the unfavorable build-up of a carbenium center at the α-position of the carbonyls, i.e. the propellane junction in **84**.



In order to still achieve the wanted bond cleavage in **84**, potassium-graphite intercalation compound (C_8K) was applied so that conjugation of the carbonyls and lateral bonds were not anymore the predominant factors for the cleavage of the cyclopropane. Similarly, a build-up of cationic intermediates will be avoided by this method which is known to proceed via diradical anions (see below). As a result, the central C-C bond in **84** was cleaved with C_8K and **85** was obtained that is according to our synthetic plan the precursor of the ABC ring skeleton of the anti-tumor drug taxol (**1**).



For introducing the C ring to the compound **85**, one of the carbonyls of **85** was protected and the monoprotected ketone **135** was subsequently transformed to *tert*-butyldimethylsilyl enol ether **136**. Next, $ZrCl_4$-catalyzed [2+2] cycloadditions with but-2-ynoicacid methylester (**133**) were studied. Unfortunately, the strong oxophilic character of the catalyst renders the [2+2] reaction of **136** and **133** very difficult to handle and the starting materials were recovered. Further attempts in this direction will be undertaken in the future by handling the reaction under strict oxygen-free conditions (glove box under argon) since analogous transformations in literature sound promising in view of further attempts to carry out this transformation succesfully.



It should also be noted that the present approach towards **1** involves – in contrast to most approaches in literature – precursors containing the geminal dimethyl group which is ultimately very important for the biological activity of the target.

2 Introduction

2.1 Short history

Taxol (**1,** Figure 1) is a natural anticancer product, which is isolated from the bark of the pacific yew tree, *Taxus brevifolia*. The activity of the compound was discovered in a screening process initiated by the National Cancer Institute (NCI) for chemotherapeutic activity. As a result of this screening process *Taxus brevifolia* was found to be cyctotoxic to 9KB (human oral epidermoid carcinoma) cells and P1534 leukemia cells by *Wani* and *Wall* who gave the name of "taxol" to this antitumor compound[1]. In 1971, they have also cleared the tetracyclic, highly oxygenated diterpene structure of taxol by obtaining the single crystal X-ray structure. Despite its promising activity and novel structure, initial interest in taxol was not great due to its scarcity, poor aqueous solubility and the lack of information about its mechanism of action. The discovery of taxol's mechanism of action by *Horwitz*[2] and finding the activity against B16 mouse melanoma cell[3] led to increased interest in taxol. First clinical trials began in 1981 and demonstrated that taxol had significant activity against solid tumors such as ovarian cancer and breast cancer, and stimulated consequence an enormous public interest in the drug[4,5]. In 1989, *Bristol-Myers Squibb* was selected to commercialise taxol. The Food and Drug Administration (FDA) approved the use of taxol for treatment of ovarian cancer in 1992 and subsequently in 1994 FDA approved taxol for breast cancer chemotherapy. Currently it is used against a variety of tumor types, including lung, head, neck cancers. Also, it has activity against small cell lung cancer, oesophagel, gastricendometrial, bladder, germ cell tumors and AIDS-associated *Kaposi*'s sarcoma[6].

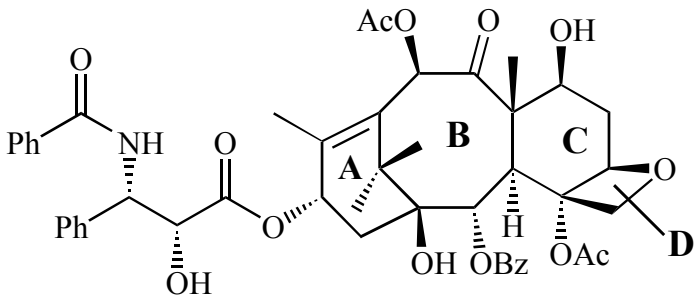


Figure 1: Structure of taxol (**1**)

2.2 Mechanism of action of taxol (1)

Taxol was discovered because of its strong cytotoxicity. Because of the supply problem and the poor aqueous solubility, some limited testing was carried out. Taxol's mechanism of action in promoting polymerization of tubulin was discovered by *Horwitz* in 1979.

Tubulin is a heterodimeric protein, consisting of two similar but distinct subunits (the α and β tubulins) which are linked to each other. Microtubules are important parts of the cell being essential for the cell division (mitosis) and they are formed by polymerisation of α- and β-tubulins (monomers). The first step of polymerization is the formation of heterodimers which come from the dimerization of one molecule of α-tubulin and one molecule of β-tubulin. For the microtubule polymerization, two molecules of guanosine 5'-triphosphate (GTP) and magnesium ions, which enhance polymerization to microtubules, are needed. Then, a nucleation center is formed by heterodimers for the further polymerization to form protofilaments which subsequently form microtubules. A normal microtubule has a diameter of 24 nm and is formed by 13 protofilaments (Figure 2).

When a cell needs to form microtubules for cell division, the rate of formation of microtubules is greater than the rate of decomposition. The concentration of tubulin decreases until it reaches the critical concentration of tubulin, there exists an equilibrium between tubulin and microtubulin.[7] This process is reversible for a normal cell. The role of taxol is to bind microtubules and stabilize them.[3] Thus, the equilibrium between tubulin-microtubulin is affected, and tubulins are converted into microtubulins irreversibly. Taxol decreases both the critical concentration of tubulin being necessary for polymerization including the induction time for polymerization[8] and taxol does it either in the presence or absence of GTP and magnesium ion. Taxol-induced microtubulins are thinner and much more stable than normal microtubules. At low temperatures and after treatment with calcium, microtubules are depolymerized but these conditions do not affect the taxol-induced microtubules. Hence, taxol blocks cells, making the formation of a normal mitotic apparatus impossible and inhibits cell division or proceeds very slowly to bring about tumor size decrease. Therefore, the best explanation of the cytotoxicity of taxol bases on its ability to disrupt the mitotic spindle.[9]

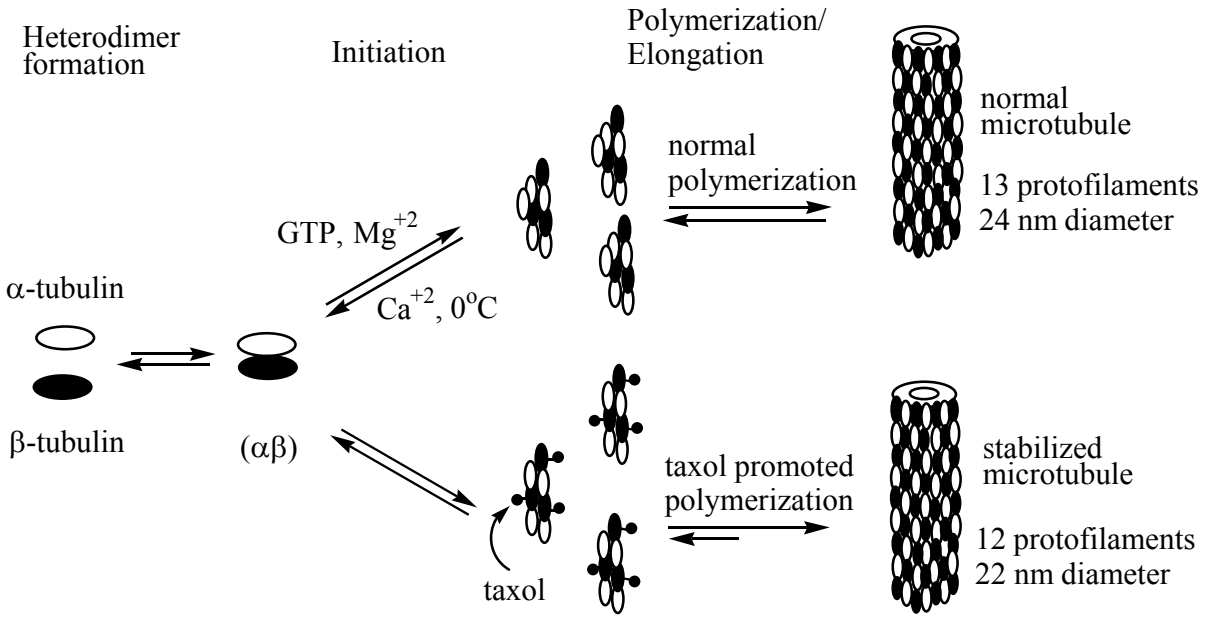


Figure 2: Tubulin-microtubule equilibrium[10]: normal microtubule assembly (upper), taxol-promoted microtubule assembly (lower)

2.3 Chemistry of taxol (1) and structure-activity relationships (SAR)

Taxol (**1**) belongs to the class of taxane diterpenoids or taxoids which are natural products. The taxane skeleton consists of a basic pentamenthyl[9.3.1.0]tricyclopentadecane skeleton and its unique numbering system is shown in Figure 3. It has mainly two differences as compared to other taxoids which are the N-benzoylphenylisoserine ester group at C-13 - known as "side chain" – and an unusual fourth ring in the form of an oxetane attached at the C-4,5 positions.

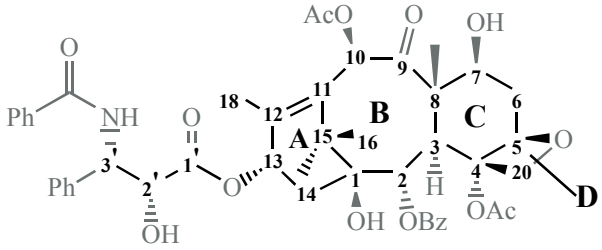


Figure 3: Numbering system of taxol (**1**)

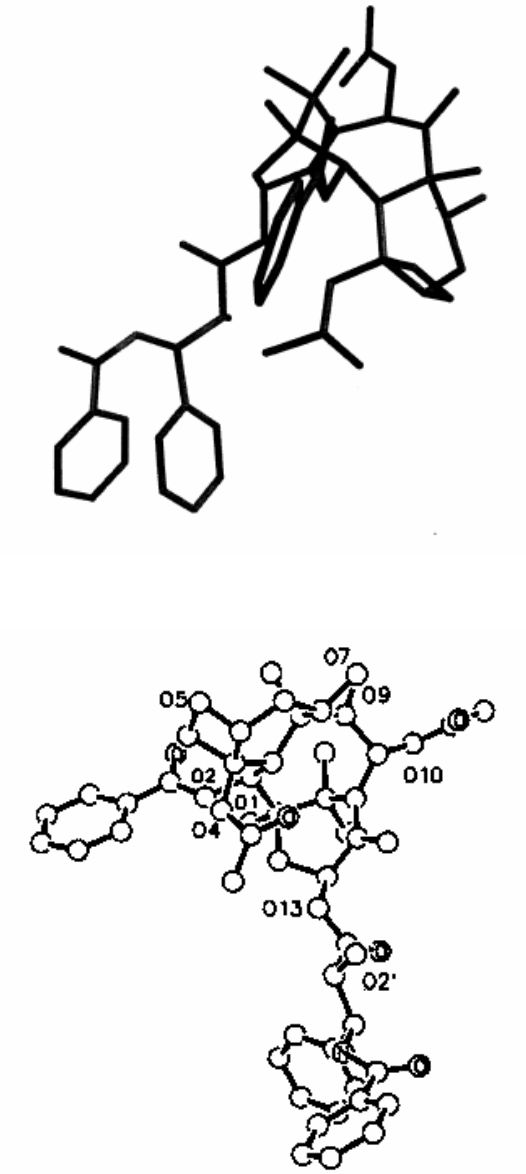


Figure 3: Two different 3D views[11] of taxol (**1**)

The structure of taxol (**1**) is quite unusual, consisting of a bridged tetracyclic skeleton with a β-phenylisoserine side chain and the conformation according to X-ray is called "inverted cup". Its molecular formula is $C_{47}H_{51}NO_{14}$ with the molecular weight of 853.92 g mol^{-1} and the IUPAC systematic name[11c] is: [2a*R*-[2aa,4b,4ab,6b,9a(a*R**,b*S**),11a,12a,12aa,12ba]]-b-(Benzoylamino)-a-hydroxybenzenepropanoic acid 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-9-yl ester.

Interactions of drugs with their receptors are very specific and the structure-activity relationship (SAR) can give valuable information about the action of a drug. Consequently, new analogs of drugs can be designed in order to get an improved drug activity. By modifying the functional groups of taxol (**1**), one at a time, it can be learned whether they are necessary for important activity of the drug.

The taxol "side chain" which is essential for the activity, is highly flexible and has different conformations depending on the medium. Studies on structure-activity relationship[12] (SAR) showed that side chains with a free hydroxyl group at the C-2' position are crucial for the activity. For example, methylated C-2' is more toxic than taxol itself and has an increased binding affinity to tubulin.[13] Furthermore, replacement of the 3'-phenyl group by small alkyl groups like methyl, decreases the activity significantly.[14] In contrast, larger groups such as isobutyl, improve the activity of taxol (**1**).

In addition, opening of the "oxetane ring" eliminates the cytotoxicity of the taxol and the tubulin assembly activity.[15] It is concluded that hydrogen bonding properties and rigidification of the taxol ring system by the oxetane ring stabilizes the taxol-tubulin complex. For example, substitution of the oxygen by sulfur decreases the activity while replacement of the oxetane ring by a cyclopropane increases the activity drastically.[16]

Modifications at the C-1, C-2 and C-4 positions which are at the "southern hemisphere" change the activity of taxol importantly. Removal of the acetoxy group from C-4 or the benzoate group from C-2 result in reduced activity as compared with taxol.[17] Interestingly, the difference in activity is modulated by the position of substituents at C-2: While 2-*p*-azidobenzoyltaxol is inactive, 2-*m*-azidobenzoyltaxol is more active than taxol.[18]

On the other hand, SAR investigations show that modifications on the northern hemisphere of taxol did not result in remarkable effects concerning the activity.[19] Consequently, the northern hemisphere of taxol does not play an important role in the binding with microtubules. The results of the SAR studies of taxol are summarized in Figure 4.

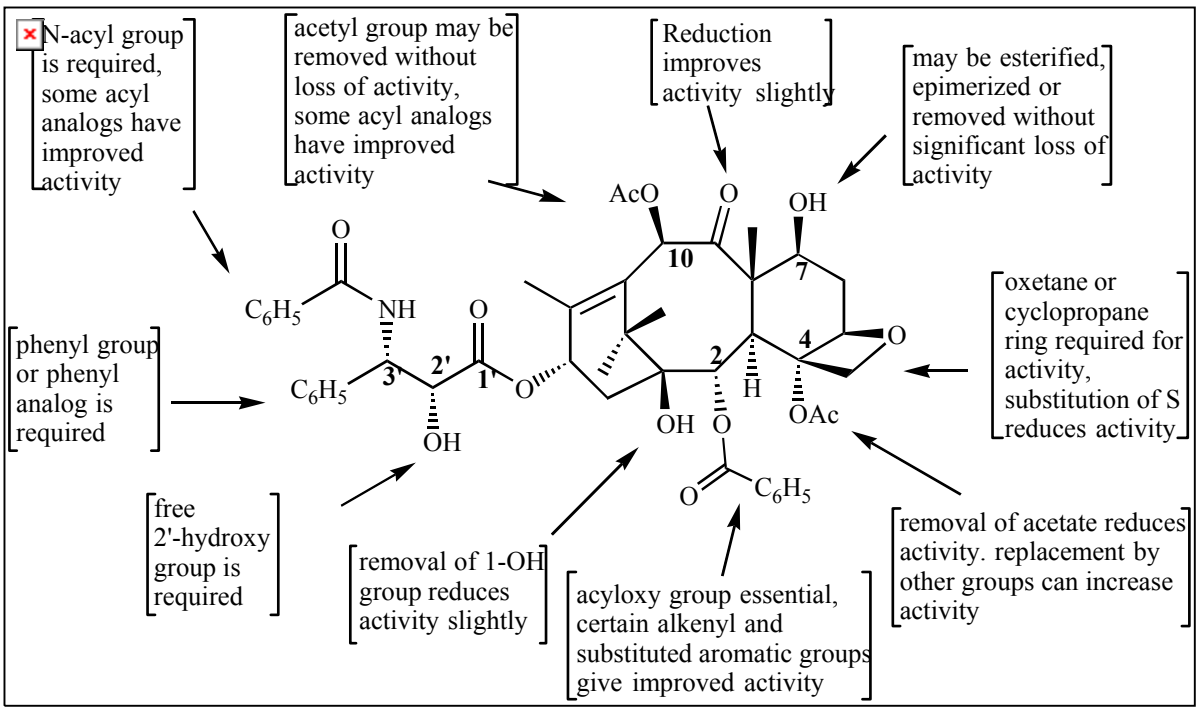
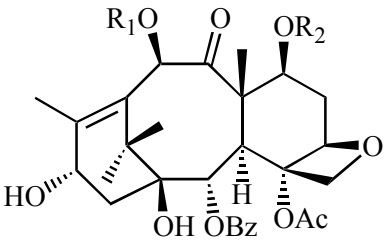


Figure 4: Some of the structure-activity relationship (SAR)[10] of taxol (**1**)

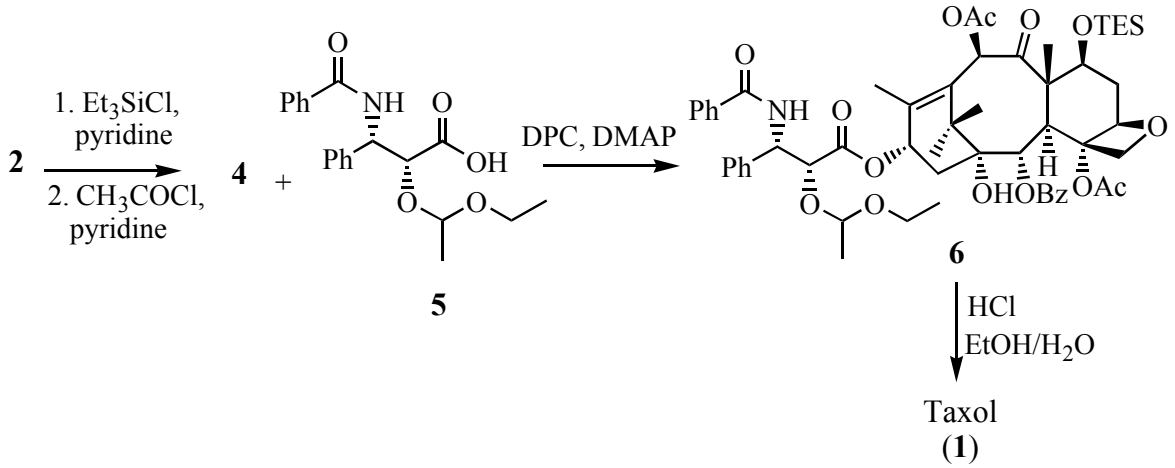
Obtaining sufficient quantities of the compound from its natural sources was one of the main problems in the development of taxol as an anticancer agent. Taxol only constitutes 0.01% of the dry weight of the inner bark of the pacific yew tree[1]. Since the typical 100 years old yew tree yields about 3 kg of bark and collection of bark kills the tree, the use of taxol from natural sources threatened the species with extinction. Therefore, chemical synthesis or bioproduction through plant tissue became an important aim for the scientists. Fortunately, it was discovered that 10-deacetylbaccarin III (10-DAB) (**2**) could be extracted from the needles and leaves of the European yew tree,[20] *Taxus baccata* in approximately 0.2% yield with small amount of baccatin III (**3**) (Figure 3).



2: 10-Deacetyl baccatin III, R_1=R_2=H
3: Baccatin III, R_1=OAc, R_2=H
4: 7-TES-Baccatin III, R_1=OAc, R_2=$SiEt_3$

Figure 5: Components for the semisynthesis of taxol (**1**)

The availability of 10-DAB provided an accessible supply for the "semi-synthetic" strategies by synthesizing the side chain[21]. There are many semi-synthetic approaches to taxol (**1**) from 10-deacetyl baccatin III (**2**) and one of these strategies[22] includes coupling of the protected side chain N-benzoyl-O(1-ethoxyethyl)-3-phenylisoserine (**5**) and 7-triethylsilyl baccatin III (**4**) which is the form of modified 10-DAB (**2**). This semi-synthetic route is applied by *Bristol-Myers Squibb* and is outlined in Scheme 1.

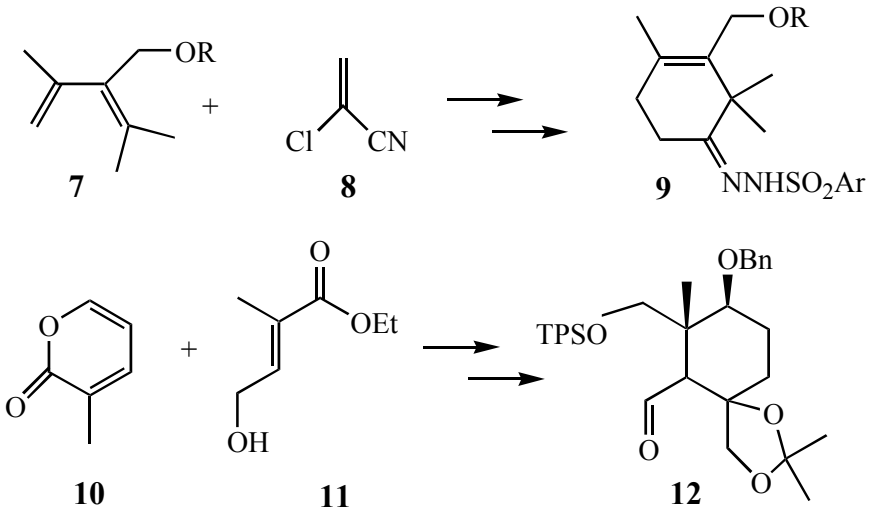


Scheme 1: Semi-synthetic approach to taxol (**1**)

2.4 Previous total syntheses of taxol (1)

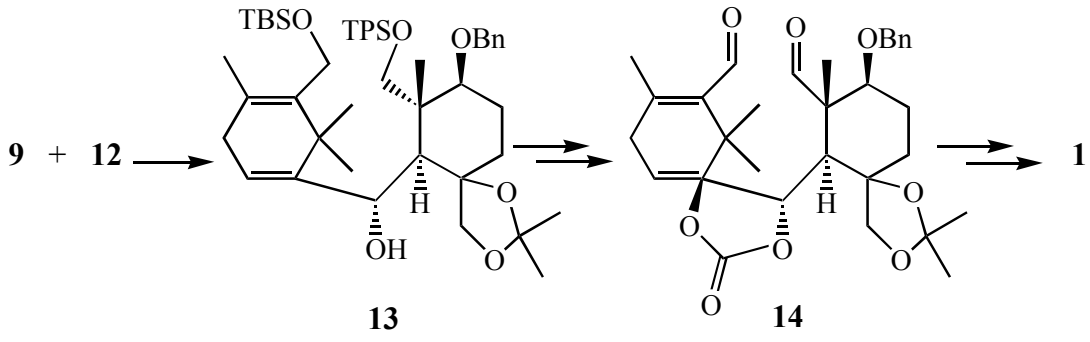
Although a "semi-synthetic" approach has the advantage of using leaves and needless which are renewable parts of the yew tree, harvesting and extraction of **2** from the tree material, however, represents a time and energy consuming problem. Thus, an intense research is being carried out to produce practical total syntheses of taxol (**1**) that would alleviate the supply problem. Because of its complex ring system and many chiral centers, six independent syntheses based on very lengthy accesses have been achieved to date by: *Nicolaou* (1994), *Holton* (1994), *Danishefsky* (1995), *Wender* (1997), *Kuwajima* (1998) and *Mukaiyama* (1999).

Nicolaou has chosen a convergent approach[23] (Scheme 2) in which rings A and C were constructed separately and then brought together to form the 8-membered B ring. Both A and B ring fragments were synthesized via the *Diels-Alder* reaction. For the regiochemistry of the C ring fragment **12**, two reaction partners, i.e. **10** and **11,** were temporarily tethered as the boronate and then decomplexed to aldehyde **12**.



Scheme 2: *Nicolaou* approach, synthesis of A and B ring fragments

One of the key steps in *Nicolaou*'s synthesis is the *Shapiro* coupling of **9** and **12** that brings A and B ring fragments together. This coupling rendered **13** which is the reactant of another key step, a *McMurry* cyclization to construct the ABC skeleton **14** (Scheme 3).

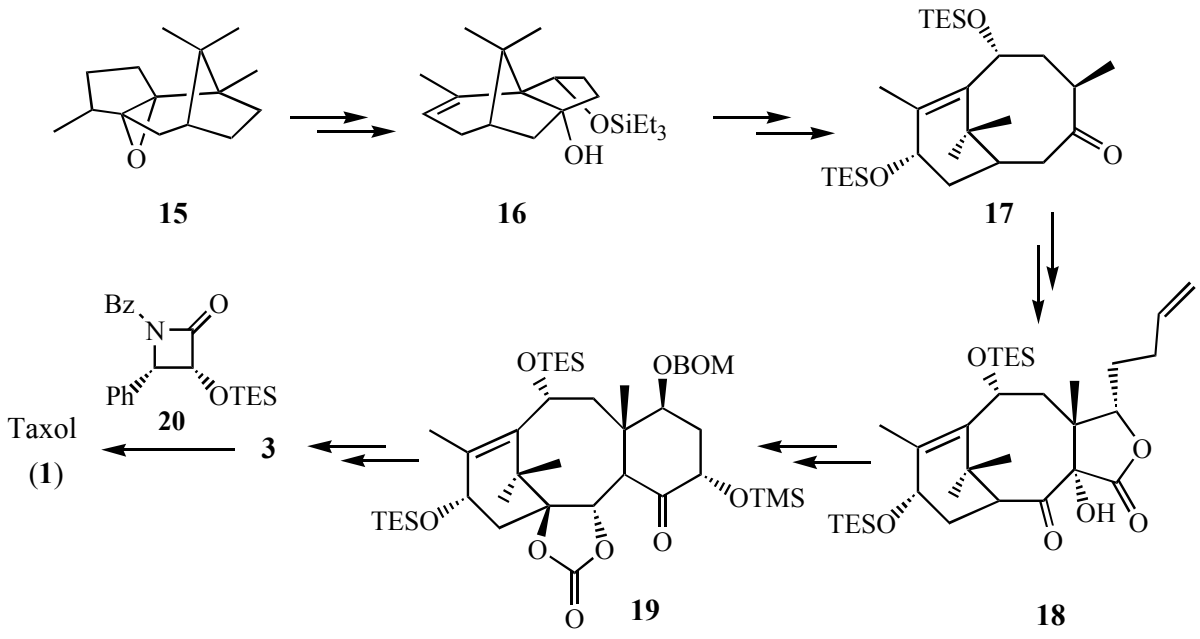


Scheme 3: Construction of the ABC rings

After *McMurry* coupling, the oxatane ring was formed. Later in the synthesis, the C-13 oxygen was introduced by chromium-mediated allylic oxidation, followed by stereospecific reduction of the enone. Coupling with the ß-lactam side chain gave taxol (**1**) in a total yield of 0,01% from commercially available materials.

Holton's approach to taxol is linear[24] (Scheme 4) which is different from that of *Nicolaou*. The strategy of the total synthesis relies on the ring enlargement of the natural product β-patchoulene oxide (**15**) to construct the AB ring system **17** by using an epoxy to alcohol fragmentation including protection. Then **17** was elaborated to the ABC system **19** through intermediate **18**. After the final elaboration of D ring and functional group manipulations, baccatin III (**3**) was synthesized.

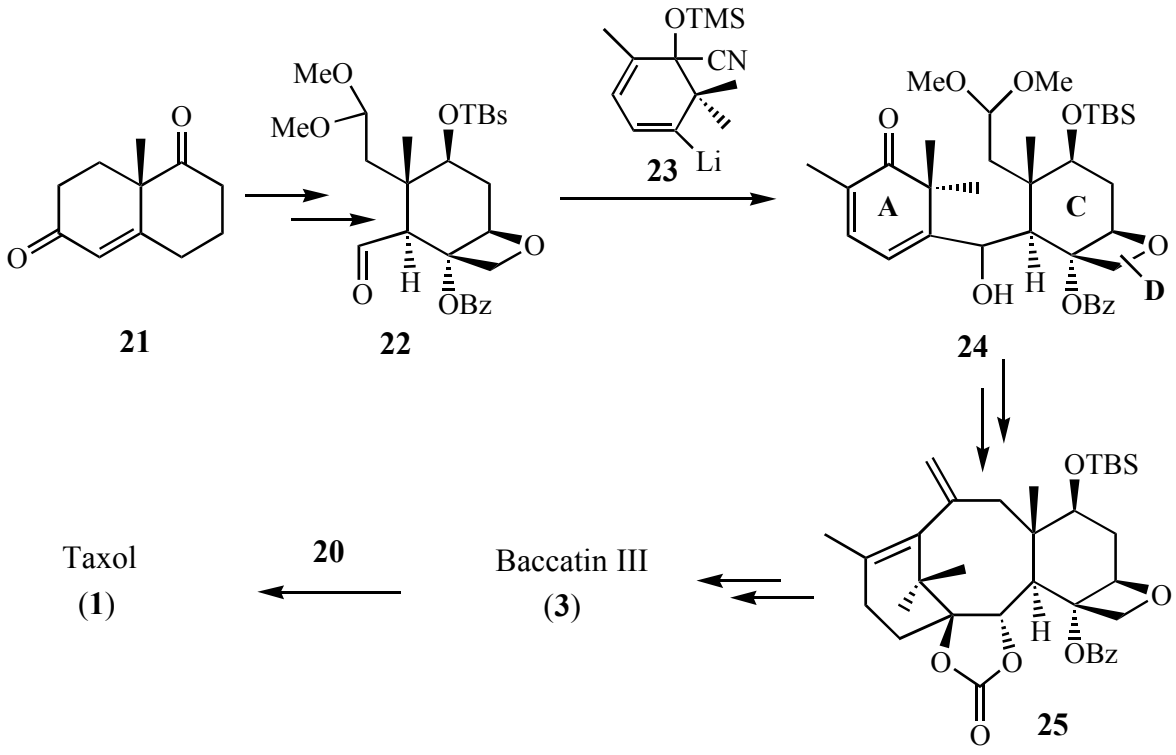
Introduction of the "side chain" was managed by coupling of **3** with β-lactam **20**, followed by further desilylation. Taxol (**1**) was synthesized by this route in a yield of 0.1% from commercially available starting materials.



Scheme 4: *Holton*'s synthetic route to taxol (**1**)

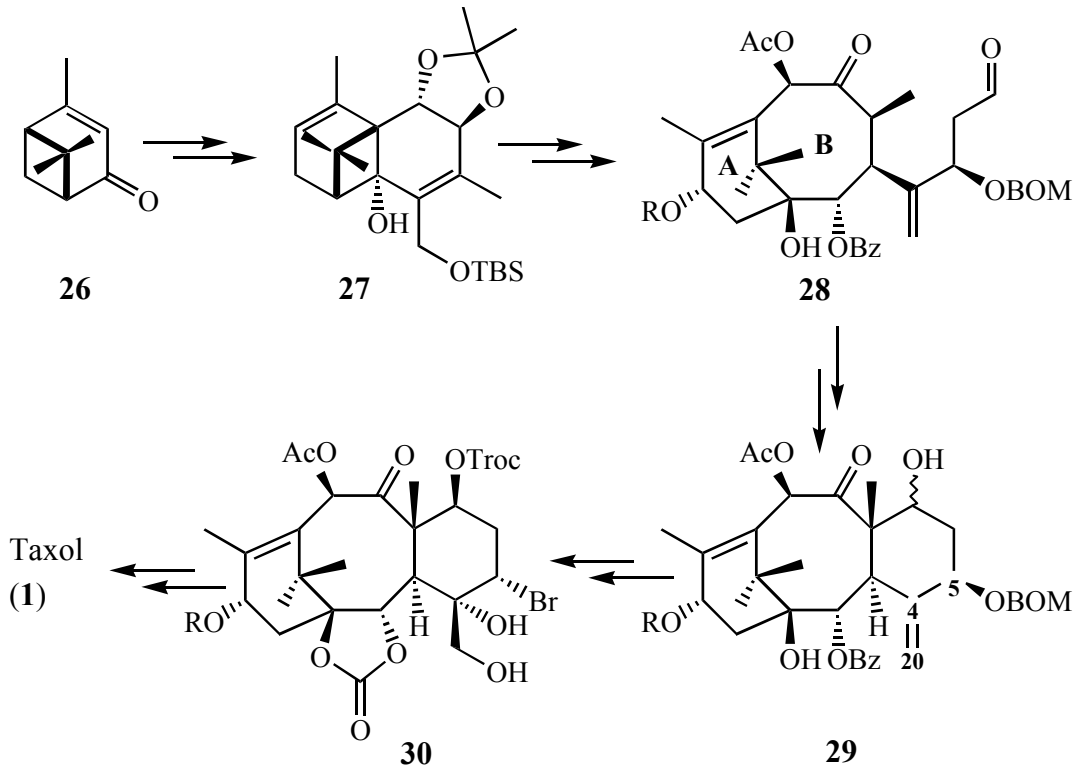
Danishefsky's convergent approach[25] is the only one to start with a preformed oxetane ring (Scheme 5). The reason for this success was having a benzyl ether rather than an acetate. For the synthesis of CD ring moiety, *Wieland-Miescher* ketone (**21**) was used as starting material.

After fragmentation (**21** → **22**) the A ring fragment **23** was introduced to construct the A-CD part **24**. Cyclization to the ABCD skeleton was achieved via intramolecular *Heck* reaction (→ **25**). After manipulating the functional groups, **24** was converted to baccatin III (**3**) which is a potential precursor of taxol (**1**). The total synthesis was completed by coupling of the β-lactam **20**, adopting the conditions that have been developed by *Ojima* before.



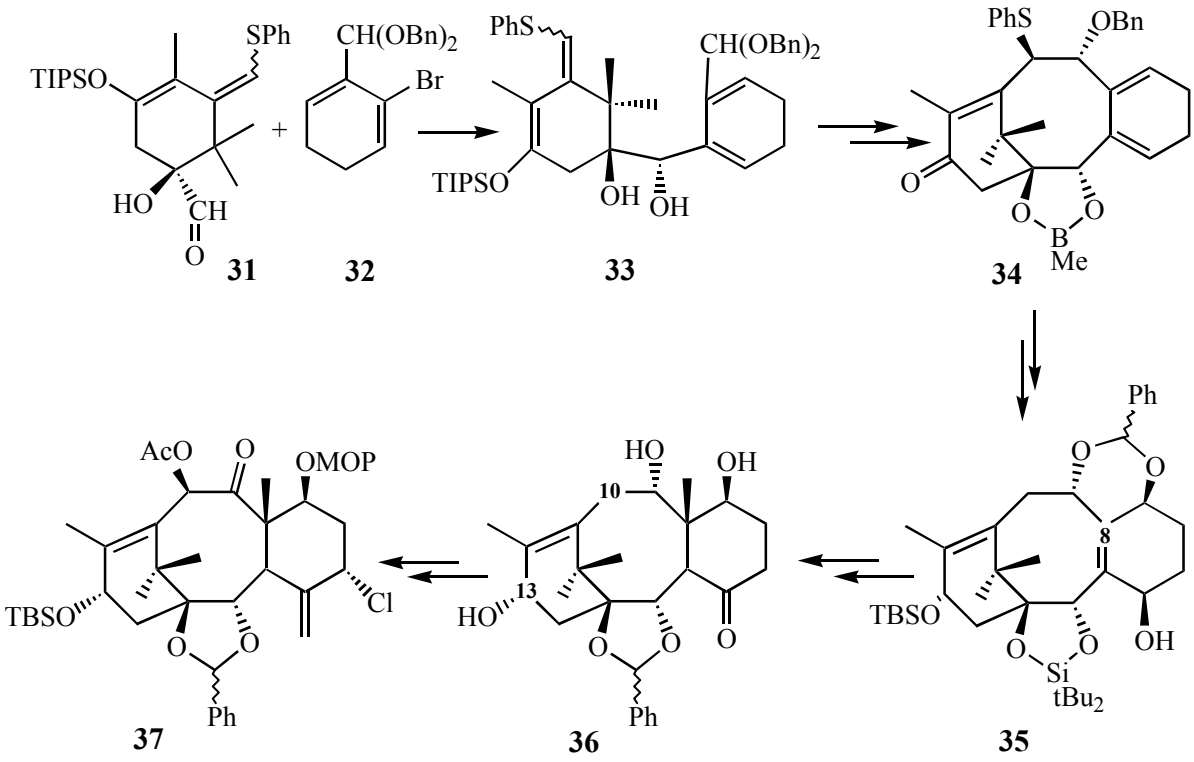
Scheme 5: *Danishefsky*'s strategy

Wender reported[26] the shortest total synthesis of taxol (**1**) to date (Scheme 6). This synthesis uses verbone (**26**) as starting material, **26** being an air oxidation by-product of pinene and it supplies 10 of the 20 carbons of the taxol skeleton. Fragmentation of epoxy alcohol **15** resulted in **28** which constitutes a fully functionalised AB system. Formation of the C ring was achieved via aldol condensation of **28** that was elaborated at the C-3 position before. After bromination of C-5, osmylation of C-4 and C-20, the oxetane ring was constructed, followed by acylation of C-4. After synthesis of 10-deacetylbaccatin III, taxol (**1**) has been reached by employing the β–lactam coupling reactions used before. The overall synthesis has 37 steps from the starting verbone (**26**).



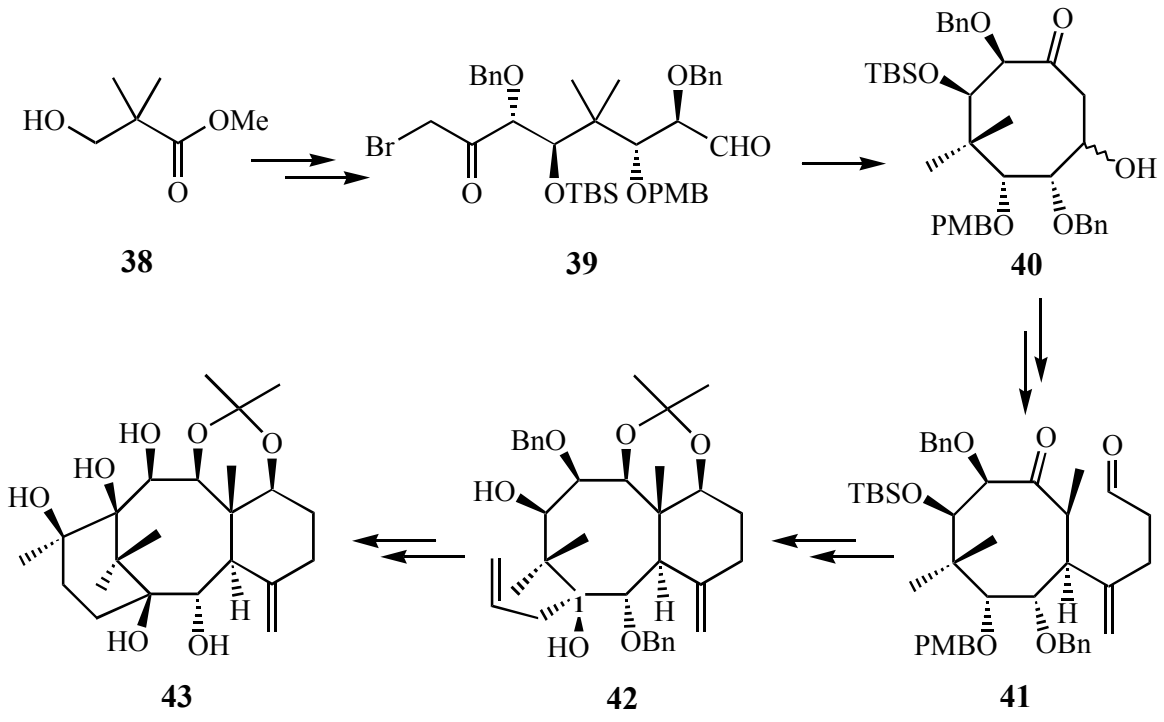
Scheme 6: *Wender*'s strategy

Kuwajima has followed a convergent route[27] to **1** (Scheme 7) like *Nicolaou* and *Danishefsky*. By a coupling reaction of the optically pure A ring hydroxy aldehyde **31** with the aromatic C-ring fragment **32** followed by Lewis acid-mediated eight-membered B ring cyclization gave the desired ABC skeleton **34**. The former fragment **31** has been synthesized from propargyl alcohol in sixteen steps and the latter fragment **32** is derived from 2-bromo-2-cyclohexenone in eight steps. Before introducing the oxetane moiety, C-8 of **35** was methylated via cyclopropanation and reductive cleavage of cyclopropyl ketone. In order to osmylate the C ring for attachment of the oxetane ring, steric congestion around the A cycle of the taxol skeleton increased by acetylation of C-10. Since these steps - introduction of methyl to C-8 and formation of oxetane ring - needed exchange of the protecting groups, the synthetic route became rather lengthy. Finally, acylation of the C-13 by the β-lactam and removing the protecting groups completed the total synthesis.



Scheme 7: *Kuwajima*'s strategy

Mukaiyama reported the final synthesis[28] in 1999 (Scheme 8). Unlike other strategies, a unique pathway starting from an 8-membered ring compound by way of B to BC to ABC to ABCD ring construction achieved the total synthesis of taxol (**1**). Compound **39** has been converted to the B ring equivalent **40** via aldol cyclization. Although 8-membered ring compounds are not easily available directly from simple linear precursors, this high yielding cyclization proceeds smoothly because the linear precursor having suitable conformations for cyclization. The C ring was introduced via *Michael* addition and intramolecular aldol cyclization to **40**. Construction of the ABC ring system was achieved by way of allylation of C-1 and an intramolecular pinacol coupling reaction of **41**. The oxetane ring was finally introduced via allylic bromination, osmylation and ultimately the addition of the side chain has completed the total synthesis.

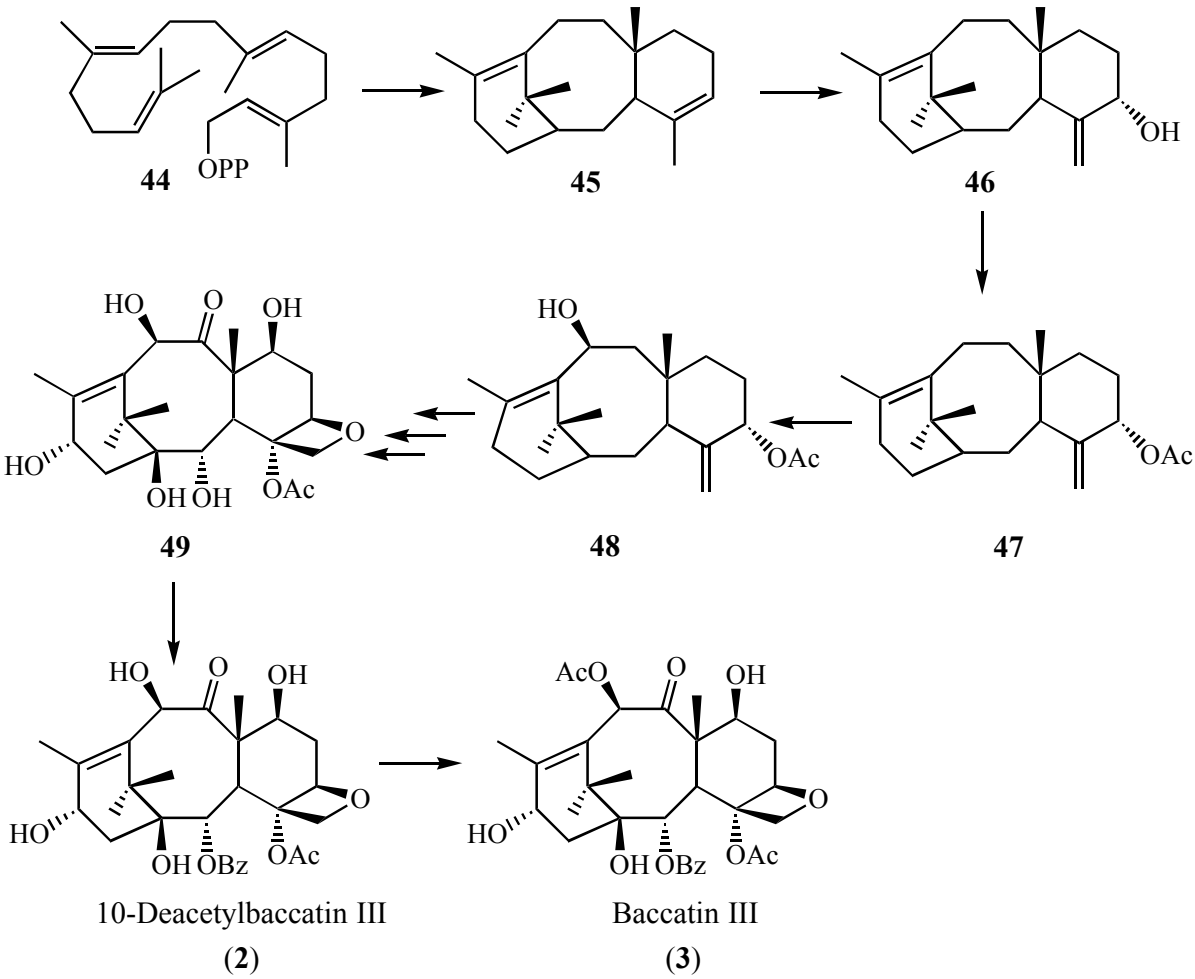


Scheme 8: *Mukaiyama*'s strategy

2.5 Biosynthetic studies

In addition to total taxol syntheses, alternative sources for taxol production are vigorously searched for due to the long reaction sequences and low yields of the hitherto synthetic approaches and the required substantial effort for purification of semi-synthesis precursors from plant tissue and separation of the desired intermediates. Improvement of the biosynthetic process based on the understanding of the pathway for taxol formation, i.e. the enzymes an their mechanism of action and the structural gene encoding of these enzymes. To date several investigations have been done for the biosynthetic approach of taxol.

The taxol biosynthetic way consists of approximately 20 enzymatic steps and it has been shown[29] that cytochrome P450 enzymes responsible for oxygenation, hydroxylation and acetylation. However, the intermediate steps of the taxol biosynthetic pathway remain undefined and are under investigation. The route to taxol (**1**) starts with the cyclization of the diterpenoid precursor geranylgeranyldiphosphate (**44**) to taxa-4(5),11(12)diene (**45**) by taxadiene synthase (Scheme 9). Then **45** is hydroxylated to taxa-4(20),11(12)-dien-5α-ol (**46**) by cyctochrome P450 taxadiene 5α-hydroxylase. **46** is subsequently converted to taxa-4(20),11(12)-dien-5α-yl acetate (**47**) by taxa-4(20),11(12)-dien-5α-ol-*O*-acetyltransferase. Hydroxylation of **47** by cyctochrome P450 taxane 10β-hydroxylase gives **48** that is converted to **49** via yet undefined steps. Taxane-2α-*O*-benzoyltransferase converts **49** into 10-deacetylbaccatin III (**2**) that is acetylated by 10-deacetylbaccatin III-10-*O*-acetyltransferase to render baccatin III (**3**).



44 **45** **46** **47** **48** **49**

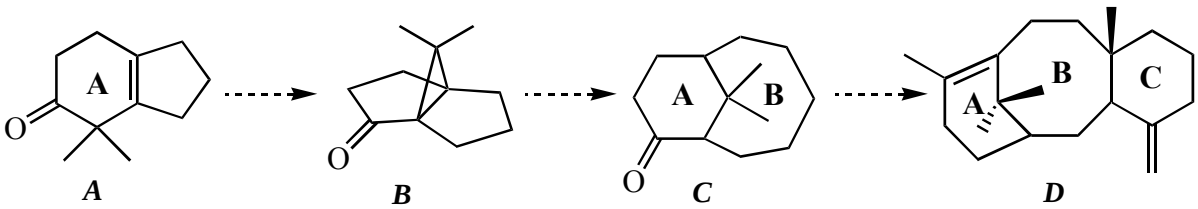
10-Deacetylbaccatin III (**2**)

Baccatin III (**3**)

Scheme 9: Biosynthetic pathways to taxol

2.6 Objectives

The aim of this work was to synthesize precursors en route to a synthesis of the anti-tumor drug taxol (**1**) skeleton. Primarily structures of types ***C*** and ***D*** should be approached as an entry to the basic ABC ring skeleton of **1**. The envisaged synthetic strategy, which is the result of a retrosynthetic analysis (see Scheme 10, p. 21 and structures below) includes two key steps that are step (a) a photochemical oxa-di-π-methane (ODPM) rearrangement of β,γ-unsaturated cyclic dienone structures of type ***A*** to afford the propellane-type cyclopropyl ketone ***B***. This intermediate should beneficially contain the characteristic geminal dimethyl pattern being seemingly important for the biological activity of **1**. A second important step (b) will involve the cleavage of the central cyclopropane bond of the propylene ***B*** (→ ***C***) for a proper set-up of the AB ring moiety.



Although the total synthesis of **1** has been achieved six times before, none of these approaches is efficient and the synthetic routes are lengthy. The shortest route consists of 37 steps (synthesis by *Wender* et al.[24]). At present, the anti-tumor drug taxol (**1**) is obtained semi-synthetically by harvesting the leaves of the European yew tree (*taxus baccata*) and extracting the 10-deacetylbaccarin III (10-DAB) (**2**) from the leaves. Since the harvesting and extracting consume lots of time and energy, the presently available supply of **1** is problematic. This work is to pioneer a shorter and efficient access of taxol (**1**) synthetically. Furthermore, the planned reaction scheme should allow to carry out a variety of functional modifications of intermediate precursors to enable broader biological activity testing of the target structures.

3 Results and discussion

3.1 Strategy

The taxane diterpenes, the main representative being taxol (**1**, Figure 1), stimulated a considerable interest from synthetic chemists because of the broad antitumor activities of this class of compounds and their unique structures which contain an unusual tetracyclic skeleton with an sp^2 carbon at its bridgehead C-11 and a geminal dimethyl group at the carbon bridge C-15 between the A and B rings. While several approaches to the total and semi synthesis of taxol have been successfully carried out.[30] many attempts have focused on the synthesis of the carbon skeleton of this diterpene.[31] The synthetic approaches are yet very lengthy and especially the achieved total syntheses out of this reason unrealistic for practical applications.

In our studies directed towards the synthesis of the basic taxol skeleton, such as **50** (see Scheme 10, p. 22), we planned a linear route as outlined in a retrosynthetic way. One of the key steps, i.e. **52** ⇒ **53**, represents synthetically a photochemical transformation, the so-called oxa-di-π-methane (ODPM) rearrangement, which involves in the present case the reaction of the β,γ-unsaturated enone **53** to **52**. The ODPM rearrangement of β,γ-enones was successfully applied to the synthesis of natural products[32] in the presence of other functional groups that are not affected under irradiation. This photochemical key step is thought to be a short entry to achieve a synthetic access to the bicyclic **51** and the tricyclic **50** on the way to **1**. To make the photochemical key step possible we should have a short access to the enone **53** which is planned along the retrosynthetic line **53** ⇒ **54** ⇒ **55**.

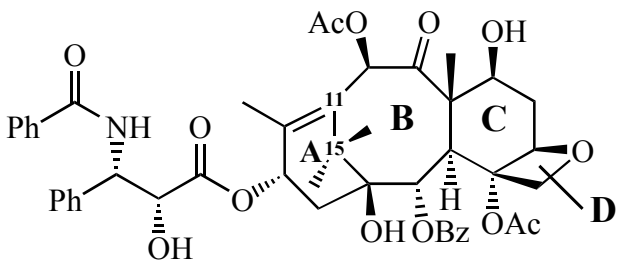
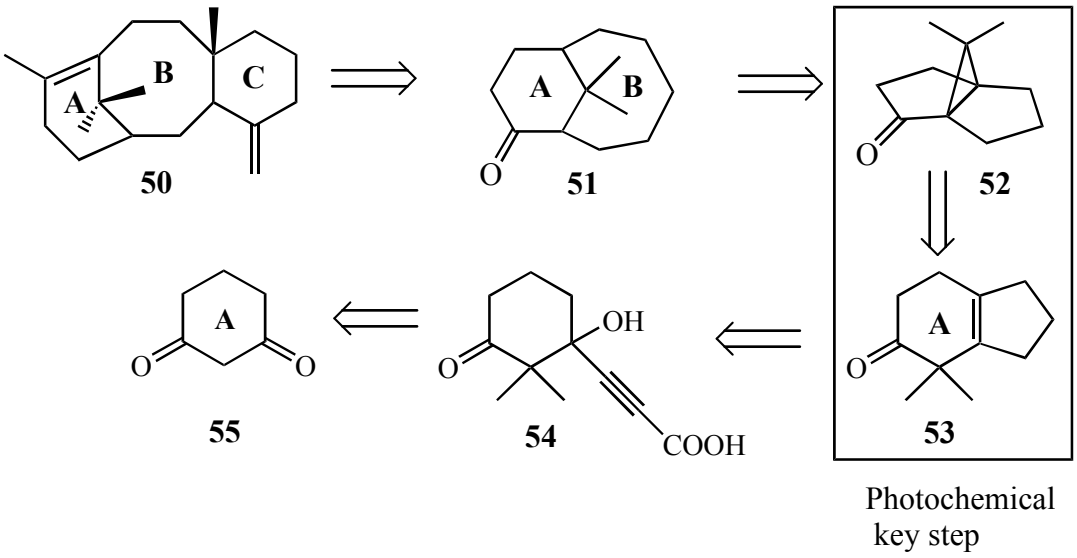


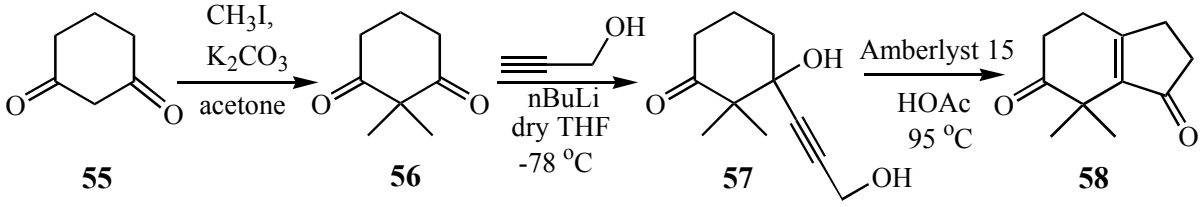
Figure 7: Structure of taxol (**1**)



Scheme 10: Retrosynthetic route to the basic taxol-like skeleton **50**

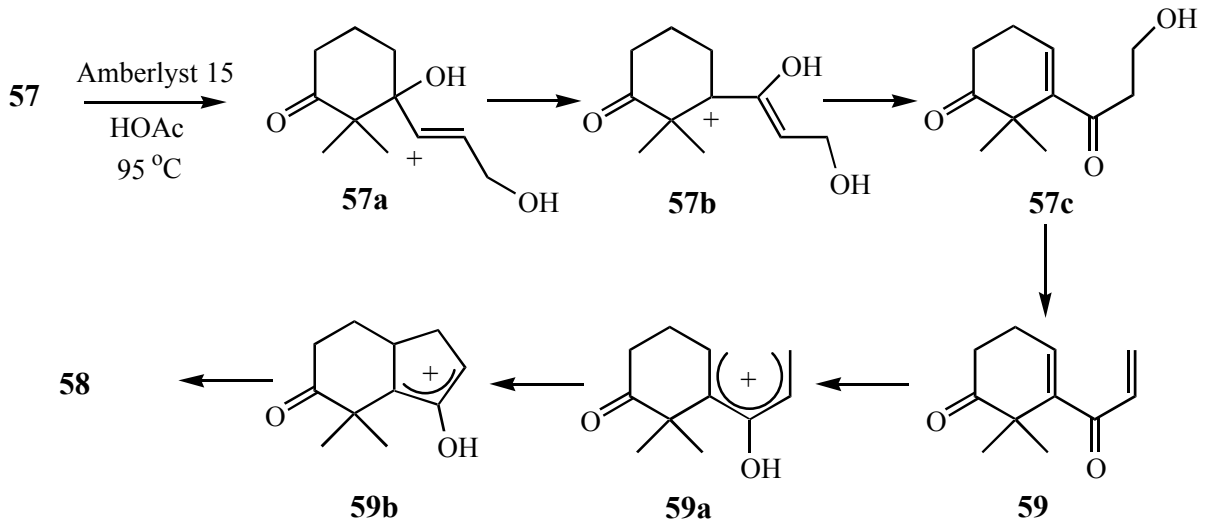
3.2 Synthesis of 2,2-dimethylbicyclo[4.3.0]non-1(6)-en-3,9-dione (58)

The retrosynthetic analysis of the diterpene skeleton **50** (Scheme 10) shows how the envisaged ODPM rearrangement strategy (**53** → **52**) relies on the access to the β,γ-enone **53** or an analog thereof. The first step of the reaction sequence for the synthesis of **58** (Scheme 11), which is a carbonyl analog of **53**, starts with dimethylation[33] of the commercially available cyclohexan-1,3-dione (**55**). Afterwards, dilithated propargyl alcohol was added to **56** at –78 ºC to give **57** in 54% yield.[34] For the synthesis of the target β,γ-endione **58**, a *Nazarov*-like cyclization was applied to **57**.



Scheme 11: Synthesis of **58** from **55**

To accomplish this *Nazarov*-type cyclization, acidic catalysts such as CH_3OH/H_2SO_4,[35] $HOAc/H_2SO_4$[36] and P_2O_5/CH_3SO_3H[33c,37] were applied which, however, resulted in decomposition of the starting material. Only the treatment with an acidic ion exchange resin, amberlyst 15 in HOAc, gave[34,32c,38] **58** from **57**, although in a low yield of 13%. The suggested mechanism of this transformation is depicted in Scheme 12.



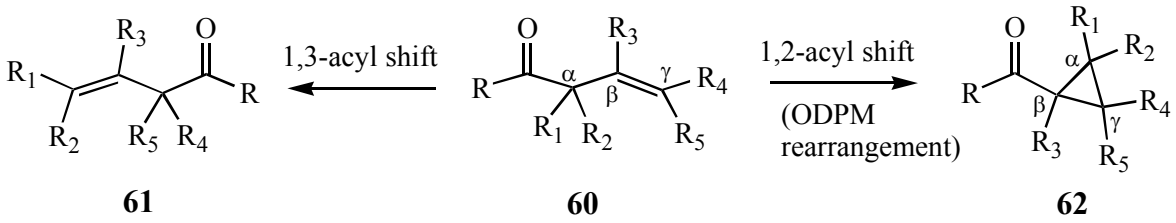
Scheme 12: The proposed reaction mechanism of the *Nazarov*-like cyclization **57** → **58**

Cyclization of divinyl ketones to yield cyclopentenones is called *Nazarov* cyclization. **59** → **58** is a typical *Nazarov* cyclization. **59** is the precursor to form the cyclic cationic intermediate **59b** on the way to **58** via the acyclic precursor **59a**. In addition, acetylenic diols can be transformed to five-membered cyclic adducts. In case of the cyclization of compound **57**, **59** is formed *in situ* by treating **57** with acidic ion exchange resin amberlyst 15 which implies the intermediacy of the vinylic cation **57a** and its rearranged isomer **57b** on the way to **59** via **57c**.

3.3 Oxa-di-π-methane (ODPM) rearrangements

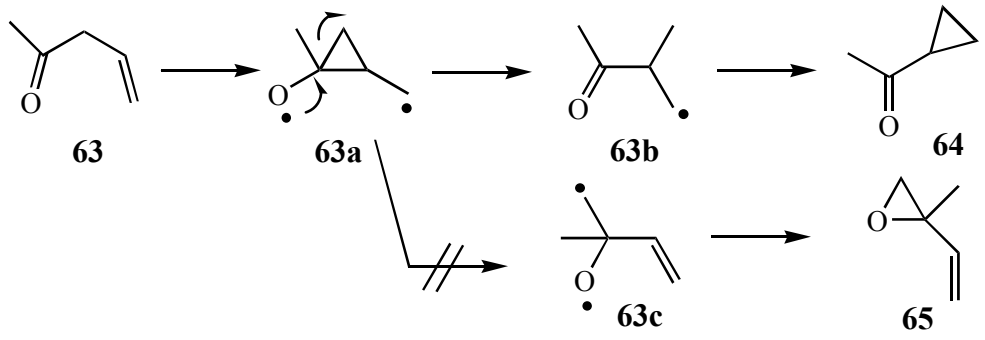
Photochemical 1,2- and 1,3-acyl sigmatropic shifts of β,γ-enones represent an important class of reactions that are often used to achieve skeletal transformations in total synthesis of natural products. The 1,2-acyl shift is commonly known as the oxa-di-π-methane (ODPM)

rearrangement since it is structurally and mechanistically analogous to the di-π-methane rearrangement.[39] In principle, β,γ-enones can undergo photoreactions such as, *cis-trans* isomerization,[40] [2+2] cycloaddition,[41] reduction,[42] decarbonylation,[43] etc. depending on the structure of the enone. However, reactions of the β,γ-unsaturated ketones are dominated by two main transformations, the 1,3-acyl shift and the ODPM rearrangement. In general, direct irradiation of β,γ-unsaturated ketones yield[44] 1,3-shifts, whereas ODPM rearrangements occur with triplet sensitized energy transfer. The former offers the isomerization of the enone (e.g. **60** → **61**), the latter results in the formation of cyclopropyl ketones[45] of type **62** (Scheme 13).



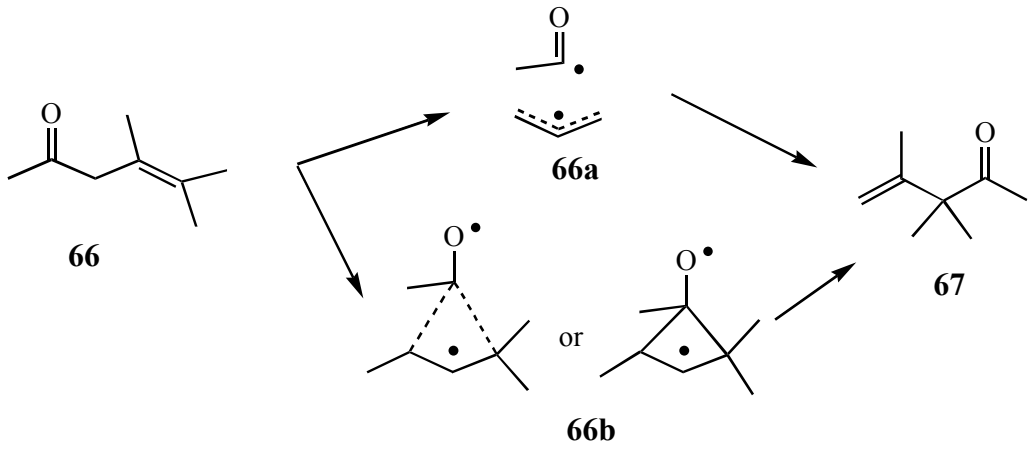
Scheme 13: 1,3-acyl shift (→ **61**) and ODPM rearrangement (→ **62**) from **60**

The ODPM rearrangement includes formally a 1,2-acyl migration followed by cyclization.[39,44] In detail, the biradical intermediate **63a** is the primary intermediate of **63** which undergoes ring opening to **63b** being a very short-lived 1,3-biradical which recombines to form the final cyclopropyl ketone **64** (Scheme 14). The alternative ring opening of the biradical intermediate **63a** that would yield the even shorter-lived oxirane **63c** has never been observed.



Scheme 14: General reaction mechanism of the oxa-di-π-methane (ODPM) rearrangement

On the other hand, two competitive routes have been proposed for the 1,3-acyl shift.[38,44] The first route is a fragmentation-recombination mechanism involving a single intermediate stage corresponding to a free radical pair **66a** which forms the final isomerization product **67** (Scheme 15). The second route is called the quasi-concerted process via the two feasible biradical intermediates **66b** which can be either a tight intermediate or a loose intermediate radical pair. In the first description of the intermediate, all C-C bonds are formed and in the second one, the radical pair is held together as a loose radical contact pair.



Scheme 15: The reaction mechanism of the 1,3-acyl shift[43]

The reaction mechanisms of the ODPM rearrangement and the 1,3-acyl shift have been studied and the excited-state reactivity and correlation has been established.[32,46] Generally, 1,3-acyl shifts can take place from the singlet excited state (S_1, $n\pi^*$) via direct irradiation, whereas the oxa-di-π-methane rearrangement occurs from the lowest triplet excited state (T_1, $\pi\pi^*$) in the presence of a sensitizer[47] (Figure 8). During irradiation, the excited state energy of a sensitizer, such as acetophenone, benzophenone or acetone, is transmitted to the β,γ-enone in the ground state which finally ends up in its lowest triplet state T_1 (π-π^*). It should be pointed out that the sensitizer must have sufficient triplet energy to excite the triplet (T_1) state of the β,γ-unsaturated ketone in an exothermic energy transfer process in order to enable the ODPM rearrangement.

Additional investigations provided more detailed information about the excited state-reactivity correlations of β,γ-unsaturated ketones. The intersystem crossing from the singlet to the triplet state populates generally the higher triplet state (T_2, ππ*) and, if the life time allows, 1,3-acyl shifts can also occur from this state. However, this represents a very rare process.[32,46]

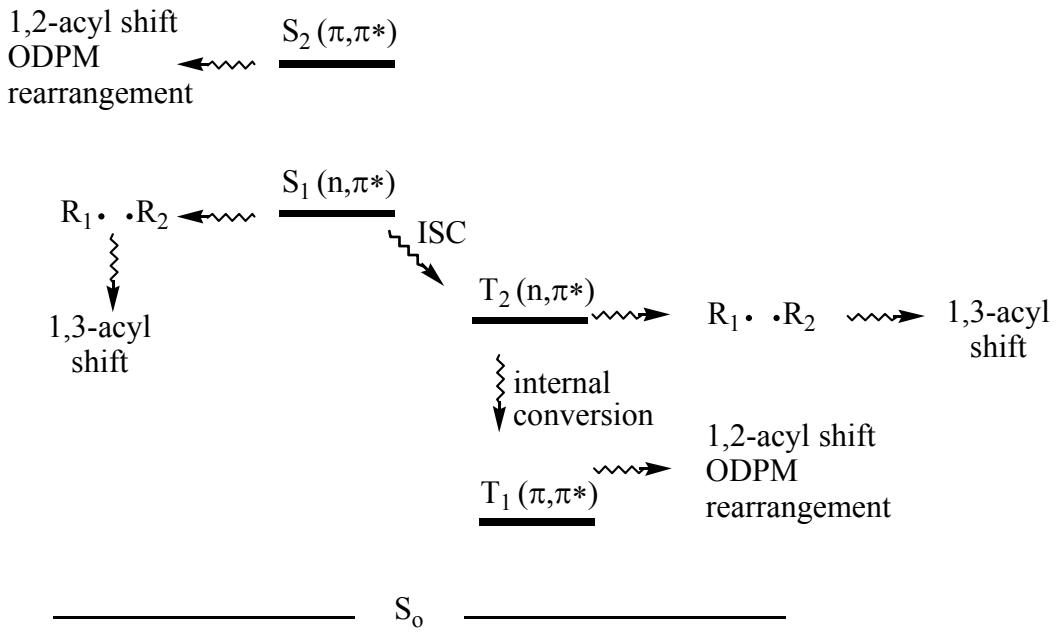
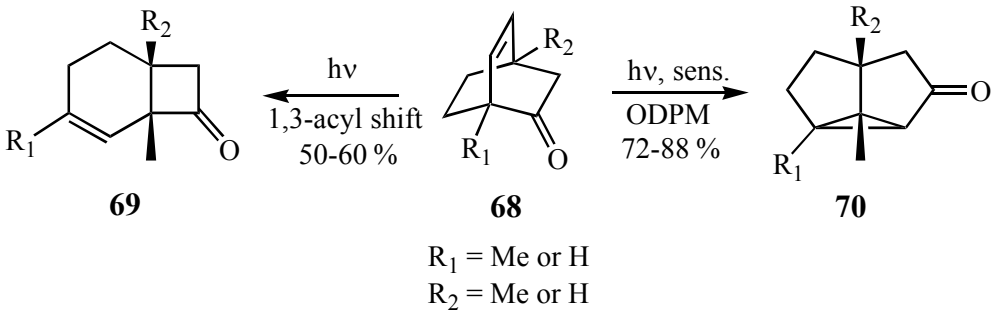


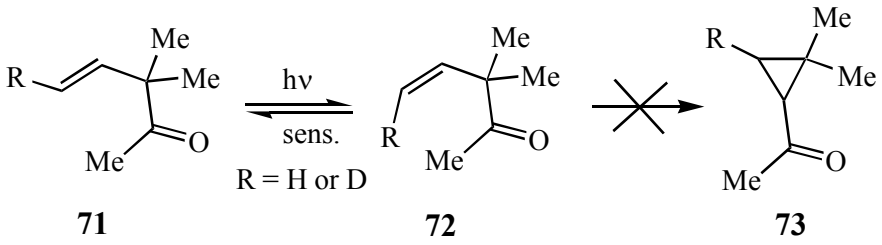
Figure 8: *Jablonsky* diagram of the oxa-di-π-methane rearrangement vs. the 1,3- acyl shift followed by rearrangement[46]

ODPM rearrangements give good to excellent yields, especially in case of the semicyclic, bicyclic and bridged β,γ-unsaturated ketones.[39b,48] The efficiency and the limits strongly depend on the conformational flexibility of the β,γ-enone moiety. For higher chemical yields, rigid structures of reactants are favorable in view of orbital overlap and inhibition of energy decay from the excited state(s) by internal conversion. The bridged, bi- and tricyclic enones exhibit such rigid structures and indeed afford ODPM rearrangements with high yields. For example, photochemical reactions of a variety of bicyclo[2.2.2]octenones have been studied.[49] Irradiation of **68** in the presence of acetone as the sensitizer gives the ODPM rearrangement products, the tricyclooctanones **70** with excellent yields up to 86% (Scheme 16). Notably, there is no scrambling of substituents observed upon this rearrangement in general. In the absence of a sensitizer the cyclobutanones **69** are obtained.



Scheme 16: 1,3-Acyl shift vs. ODPM rearrangement of the conformationally rigid bicyclic enone **68**

In order to provide sufficient rigidity in acyclic enones, the carbon between alkene and the carbonyl group of a β,γ-enone must be fully substituted by alkyl, phenyl or vinyl moieties. Otherwise, other channels of energetic deactivation of the triplet state predominate, such as *cis-trans* isomerization. This form of energy dissipation[50] is called "free-rotor effect." One example for this kind of process is shown in Scheme 17. Irradiation of **72** in the presence of a sensitizer results in *cis-trans* isomerization of **71** and **72**, without formation of an ODPM product (e.g. **73**).



Scheme 17: Free-rotor effect: *cis-trans* isomerization of **71**

Besides that, additional conjugation of chromophores at either the ketonic or the olefinic part as well as intramolecularly competitive electronic effects have been examined.[46] n general, reactants that have chromophores like **A** and **B** (Figure 9) need a sensitizer for the ODPM rearrangement, while reactants having chromophores like **C** and **D** undergo ODPM rearrangements upon direct irradiation via intersystem crossing from the singlet state (S_1, $n\pi^*$) to the triplet excited state (T_1, $\pi\pi^*$). Furthermore, ODPM reactions occur exceptionally

from the higher singlet excited state (S_2, $n\pi^*$) which is exemplified by a β,γ-enone that carries a phenyl moiety.

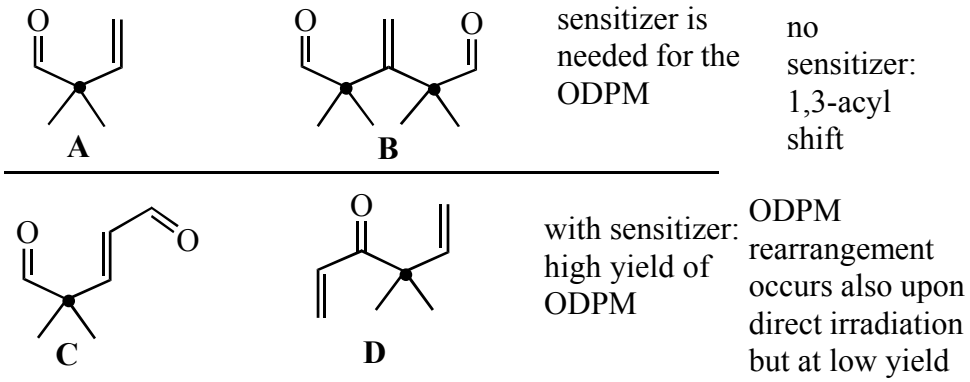


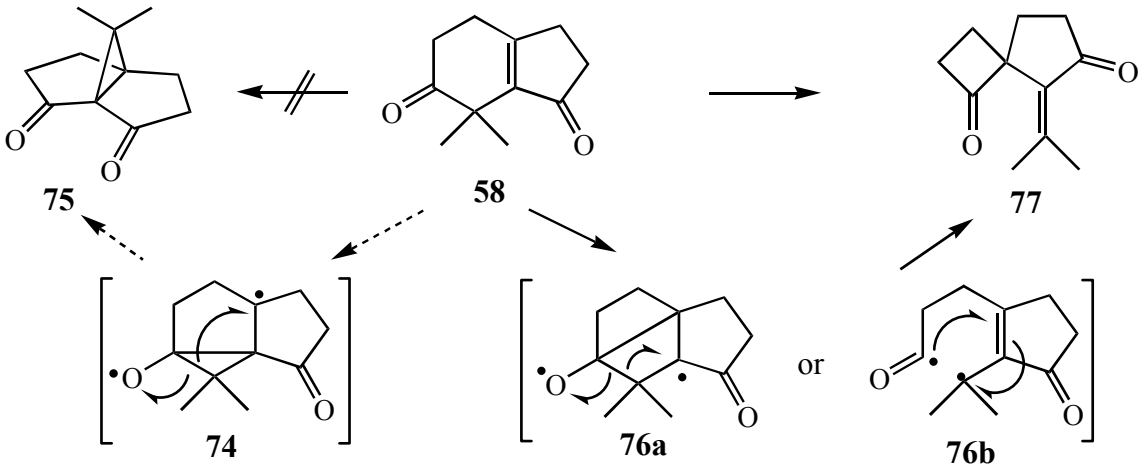
Figure 9: Chromophore conjugations: **A** and **B** undergo ODPM rearrangements in the presence of a sensitizer, **C** and **D** give low yield ODPM rearrangements without sensitizer

3.4 Photorearrangements of 58 and 78

3.4.1 Attempted ODPM rearrangement of 58

The β,γ-endione **58** (for the retrosynthetic route, see chapter 3.2, p. 22) served as the starting compound for the planned photochemical rearrangement.[31] Irradiation of **58** (Scheme 18) in the presence of acetophenone as sensitizer with 350-nm light (*Rayonet* reactor) gave a product showing NMR data not being compatible with the expected 9,9-dimethyl tricyclo[3.3.1.$0^{1,5}$]nonan-2,6-dione (**75**). Finally, the reaction product was assigned as 5-isopropylenespiro[3.4]octan-1,6-dione (**77**) according to ^{1}H, ^{13}C and the two-dimentional NMR spectra. The unsymmetric signals in the ^{1}H NMR and the existence of olefinic carbons in the ^{13}C NMR spectra proved the structure of the product **77**. Besides **77**, starting material **58** was recovered in 16% yield. According to the anticipated ODPM rearrangement mechanism, two possible diradical intermediates (**74** and **76a**/**b**) can be formulated. The lack of the expected product **75** via **74** can be explained by the stabilization of the radical intermediate **76a** by the neighboring carbonyl group. This stabilization renders this biradical energetically more favorable. Thus, instead of the expected product **75**, the spirocyclic

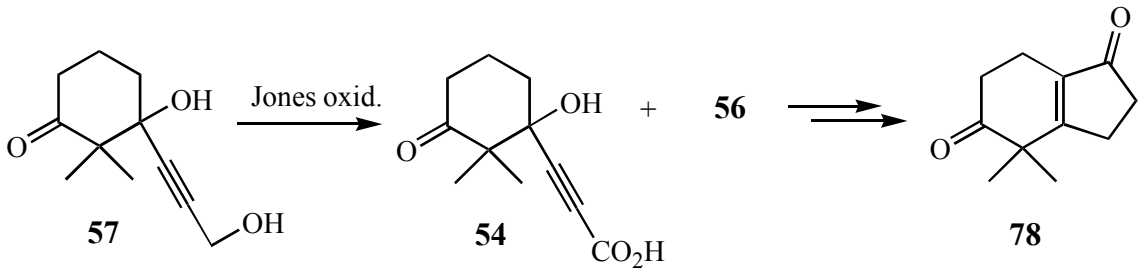
compound **77** was obtained as a result of cyclobutane cleavage in **76a**. Alternatively, the rearrangement **58** → **77** could be formulated as a 1,3-acyl shift via **76b**.



Scheme 18: The proposed reaction mechanisms of the photoreaction of **58** to **75** (not formed) and **77**

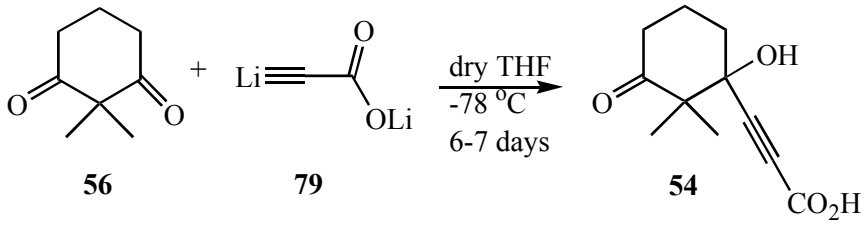
3.4.2 Successful ODPM rearrangement of 78

After the failure of the ODPM rearrangement of **58** to **75**, the synthetic route was modified and 2,2-dimethylbicyclo[4.3.0]non-1(6)-en-3,7-dione (**78**) was synthesized (Scheme 19) to probe its photochemistry which is assumed to differ significantly from that of **58**. With compound **57** in hand (Scheme 11, p. 22), we have converted it into carboxylic acid **54** via Jones oxidation[51] in a yield of 65% along with **56** (18% yield).



Scheme 19: *Jones* oxidation of **57**

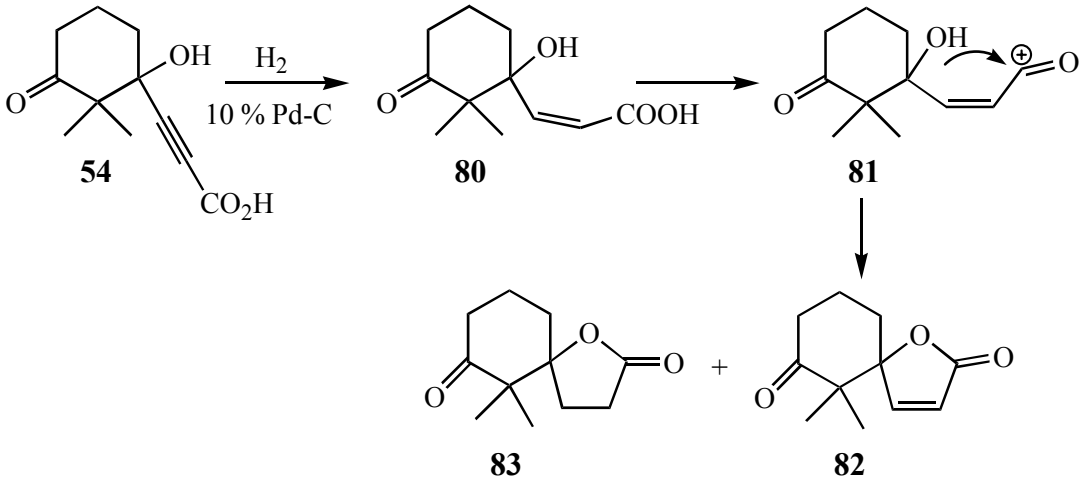
On the other hand, the carboxylic acid **54** can be synthesized directly from 2,2-dimethylcyclohexan-1,3-dione (**56**) by adding dilithated propylate **79** (Scheme 20), adopting the reaction conditions for **56** → **57**. However, a longer reaction time is needed in this latter procedure giving **54** in a slightly lower yield (59%).



56 **79** **54**

Scheme 20: Direct synthesis of **54** from **56** by addition of dilithated propargilic acid (**79**)

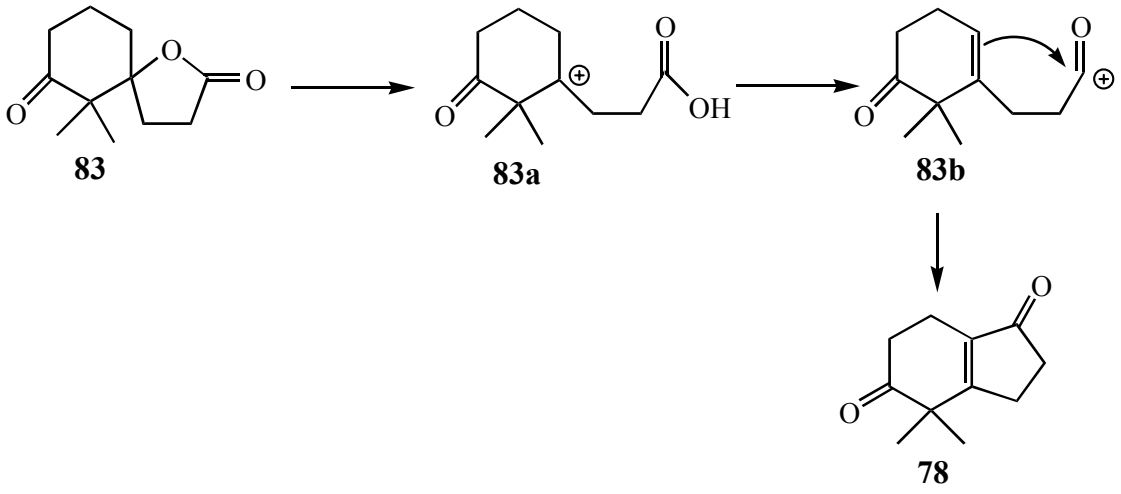
The adduct **54** was then subjected to catalytic hydrogenation[52] without further purification to synthesize lactone **83** in an overall yield of 41% from **56**. When the hydrogenation reaction time was shortened, spirolactone **83** was obtained besides the unsaturated lactone **82**. This means that the reaction proceeds via hydrogenation of the triple bond (→ **80**) followed by cyclization to **82** which upon further hydrogenation leads to **83**. Two olefinic doublets at 6.11 and 7.40 ppm in the ^{1}H NMR and –CH signals at 122.27 and 156.08 ppm in the ^{13}C NMR confirm the intermediacy of **82**.



54 **80** **81** **83** **82**

Scheme 21: Hydrogenation of **54**

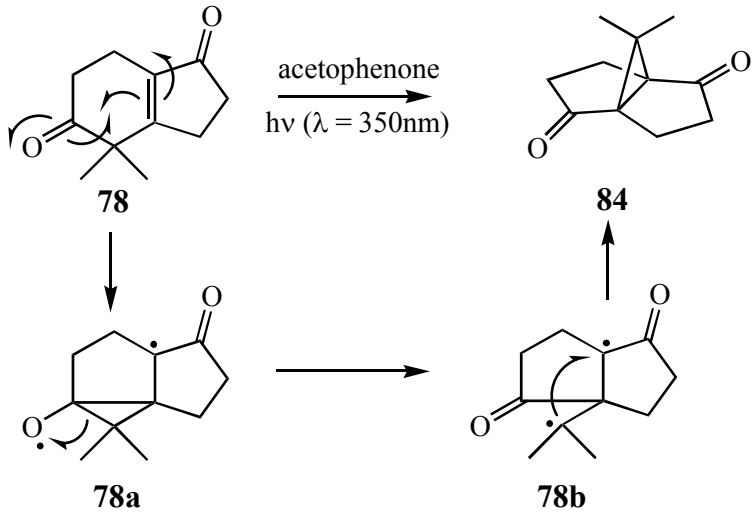
Spirolactones in general undergo rearrangement in the presence of strong acids.[37] For the synthesis of the endione **78** as substrate for the planned alternative ODPM rearrangement, cyclic lactone **83** was treated with concentrated acid which is either polyphosphoric acid[53] (PPA) or *Eaton*'s reagent[54] (P_2O_5/$MeSO_3H$). As a result of these treatments, product **78** was obtained in yields of 60% and 40%, respectively. The anticipated reaction mechanism is shown in Scheme 22. Upon opening of the spirolactone **83** carbenium ion **83a** is formed prior to elimination to **83b** which undergoes cyclization/elimination to afford ultimately the desired mixed endione **78**.



Scheme 22: Rearrangement of spirolactone **83** to the mixed endione **78**

After the synthesis of **78**, its ODPM rearrangement was explored. As mentioned before, β,γ-enones can undergo under certain circumstances ODPM rearrangements without sensitizer. However, such rearrangements under these excitation conditions are real exceptions. Although the compound **78** has a chromophore being further conjugated with the β,γ-enone moiety, the previous studies in our laboratories show that irradiation[55] of **78** without sensitizator gave the expected product **84** (Scheme 23), albeit in 8% yield only. During the attempts to increase the yield in different solvents and in the presence of sensitizaters, 40% yield of ODPM product was achieved when the reaction was run in acetonitrile and acetophenone was added as sensitizer. Moreover, by increasing the reaction time to 30 hours, the product yield increased up to 88%. Irradiation of the reaction mixture was studied by using a *Rayonet* equipment with λ_{max} = 350 nm. The likely mechanism of the photochemical

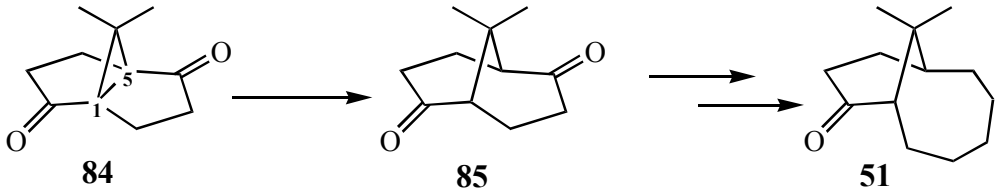
transformation of **78** → **84** is depicted in Scheme 23. After energy transfer from acetophenone to the α,β- and β,γ- unsaturated ketone **78**, biradical **78a** is generated and it rearranges to the cyclopropyl diketone **84** via recombination of the radical centers in **78b**. Notably, the spirocyclic product **77** did not form here.



Scheme 23: ODPM rearrangement of the endione **78** to **84** via the biradical intermediates **78a,b**

3.5 Attempts to cleave the central C-C bond of 84

In the studies directed towards the photochemical construction of the basic carbon skeleton of taxol (**1**), we have synthesized successfully the key intermediate 9,9-dimethyltricyclo[3.3.1.$0^{1,5}$]nonan-2,6-dione (**84**) via an ODPM rearrangement from 2,2-bicyclo[4.3.0]non-1(6)-en-3,7-dione **78** in excellent yield, and expected then to be able to open the central C-1,5 bond of this propellane product so that we can obtain bicyclo[3.3.1]nonan-2,6-dione **85** as a potential precursor of the AB rings of the taxol skeleton (→ **51**).



Scheme 24: Planned route to a precursor (**85**) of the AB rings of the taxol skeleton **51**

Cyclopropane, the smallest cycloalkane, is highly strained and has bond angles of 60°, far away from the 109.5° angle that sp^3-hybridized carbons normally adopt. Because of the bond angle compression it is seen that orbitals overlap neither head to head like in σ bonds nor laterally like in π bonds. Thus, bonds are in between σ and π bonding, called "bent bonding". The result is that the carbon-carbon bonds are weaker than those having normal bond angles and hence cyclopropanes are much more reactive than other cycloalkanes. Controlled cleavage of cyclopropane intermediates provides a useful method and has been successfully employed in the synthesis of multicyclic natural products.

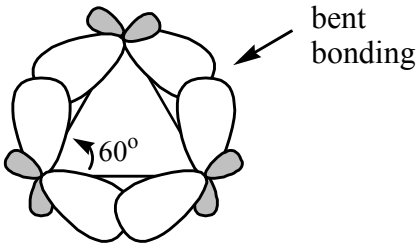
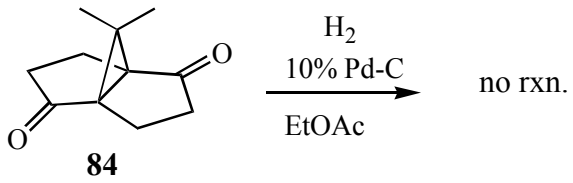


Figure 10: Bent-bonding and the interaction of σ and π orbitals of the cyclopropane

3.5.1 Hydrogenation of 84

Hydrogenation[56] of cyclopropane is one of the ways to cleave this strained cyclic compound. It has been shown that hydrogenation of cyclopropane derivatives usually results in the preferential cleavage of the least substituted ring bonds.[57] For the ring opening insertion of the catalyst, such as palladium, is needed, i.e. the steric effect plays a most important role. 9,9-dimethyltricyclo[3.3.1.$0^{1,5}$]nonan-2,6-dione (**84**) should be an excellent candidate for such a cleavage with its C_2 symmetry with a fully substituted cyclopropane. However, the

geminal dimethyl group at C-9 and the two five-membered rings seemingly protect this substrate against hydrogenation so efficiently from either side that no hydrogenation of the cyclopropane was found and complete recovery of starting material was the result when hydrogenation was carried out with 10% Pd/C in ethyl acetate.

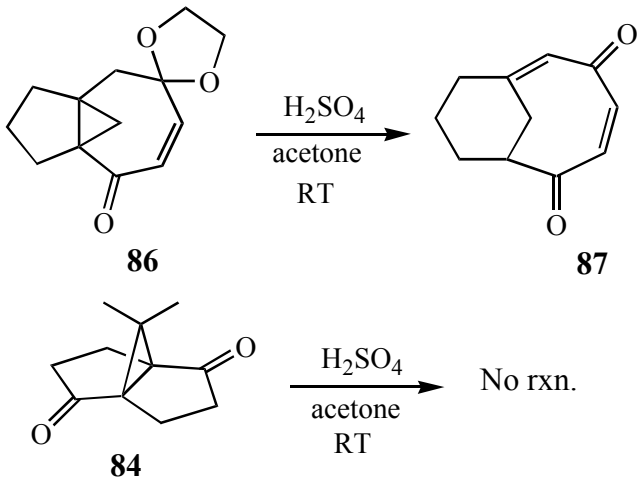


84

Scheme 25: Hydrogenation attempt of cyclopropyl diketone **84**

3.5.2 Acid-catalyzed treatment of 84

In addition to the catalytic hydrogenation of cyclopropanes, acid-catalyzed reactions are used[58] for opening of cyclopropane rings. For example, H_2SO_4/acetone was used as the cleaving agent for **86** in our laboratories effectively[59] (Scheme 26). But the same conditions applied to **84** led only to the recovery of the starting material.

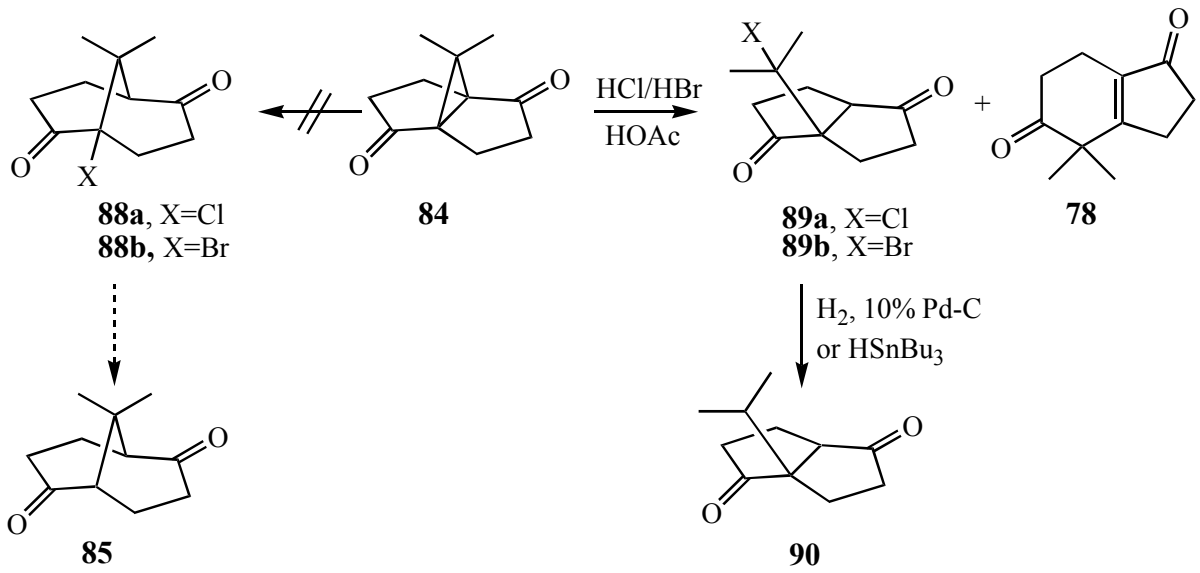


86 **87**

84

Scheme 26: Previous cyclopropyl opening (**86** → **87**) and application of the same procedure to **84**

Furthermore, electrophilic reagents were used for the cleavage of conjugated cyclopropyl ketones. **84** was treated with halogenic acids[60] (HCl or HBr) in acetic acid at reflux temperature and two compounds were obtained. The yield was increased up to 80% by using tetrachloromethane as solvent at room temperature. One of them was identified as **78** (structure, see p. 32) by its NMR analysis, whereas the other one shows NMR and mass spectral data not being compatible with the expected ring opening compounds **88a/88b** (Scheme 27). 400 MHz ^{1}H, ^{13}C NMR and IR spectra of these products fit however the structures for the halogenated compounds **89a/89b**. Both, the chlorinated and the brominated compound exhibit NMR spectra having doublets of doublets at 3.15 and 3.19 ppm, respectively. In addition, in the ^{13}C NMR spectrum the existence of two quaternary and one –CH carbons are compatible with the proposed structures **89a/89b**. In order to make sure that we have obtained **89a** and **89b** instead of the expected **88a** and **88b**, these halogenated products were subjected to dehalogenation by catalytic hydrogenation and Bu_3SnH. Unfortunately, the product does not show the NMR data being characteristic for **85**, but the existence of a quartet in the ^{1}H NMR showing the coupling of two identical methyl groups with –CH together with an unsymmetric ^{13}C NMR spectrum showing that the unexpected product **90** was obtained. These data were completed with mass spectral information to ensure that **89a/89b** were formed as a result of exclusive lateral bond cleavage of the cyclopropane.



88a, X=Cl
88b, X=Br

84

89a, X=Cl
89b, X=Br

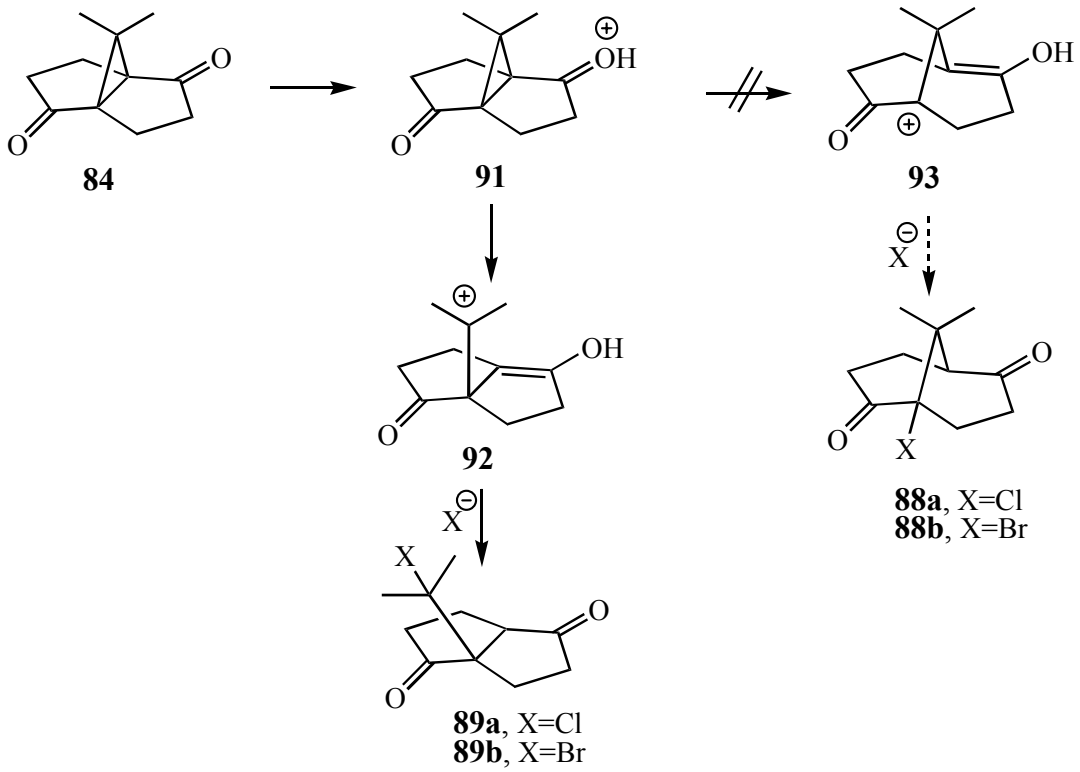
78

85

90

Scheme 27: Treatment of **84** with HCl/HOAc and HBr/HOAc

A reasonable mechanism for the acid-catalyzed opening of a cyclopropyl ketone involves initial protonation of the carbonyl group (→ **91**), followed by ring opening (→ **92**) to yield the halogenated diketones **89a** and **89b**. In theory, ring cleavage in the tricyclic diketone can yield two different bicyclic skeletons by either cleavage of central (→ **93**) or the lateral (→ **92**) bonds (Scheme 28). There are some reasons for the failure of the central bond cleavage. It is well known that formation of carbocations are difficult or impossible at bridgehead positions where they cannot be planar, i.e. adapt sp^2 configuration. Additionally, formation of bridgehead carbocations is possible only with large rings or in adamantane. Furthermore, the formation of a carbocation at α-carbons of carbonyls renders the intermediate energetically unfavorable.



Scheme 28: Anticipated reaction mechanism for the formation of **89a** and **89b** from **84**

Besides the developing carbocationic character, direction of cleavage of the cyclopropyl ketones is controlled by geometrical factors. As mentioned before, cyclopropanes have bent-bonds that have characteristics between σ and π bonds. These bent-bonds have in the present case delocalization with the π orbitals of the carbonyl groups. Owing to the geometry of the

ring system, the central carbon-carbon bond does not overlap largely with the π system of the carbonyl groups, whereas the lateral bond has excellent overlap. Thus, the cyclopropane bond with greatest overlap with the carbonyls cleaves preferentially, i.e. **84** → **92** in Scheme 28 and Figure 11.

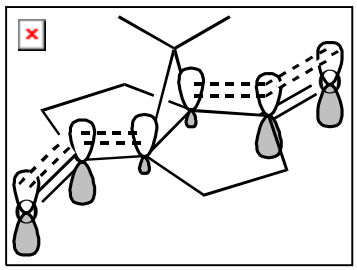
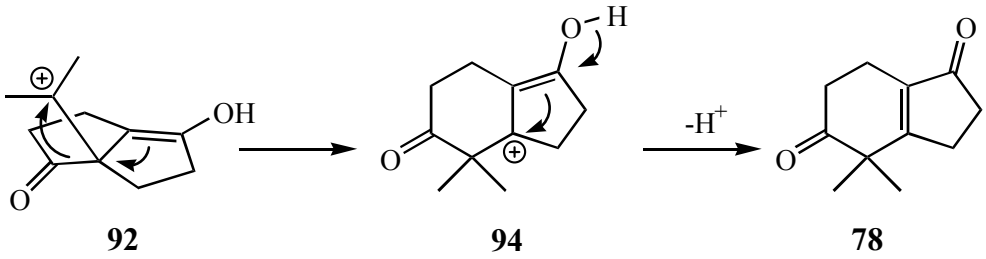


Figure 11: Interaction of orbitals of the carbonyl and the lateral bonds of the cyclopropane in **84**

The side product **78** is likely the result of carbocation rearrangement in **92** to form the α,β;β,γ- endione **78** after proton loss from **94** (Scheme 29). Interestingly, the acid-catalyzed re-formation of **78** from **84** constitutes overall a thermal retrosynthetic process (in cationic intermediate steps) of the photochemical ODPM rearrangement **78** → **84** (Scheme 23).

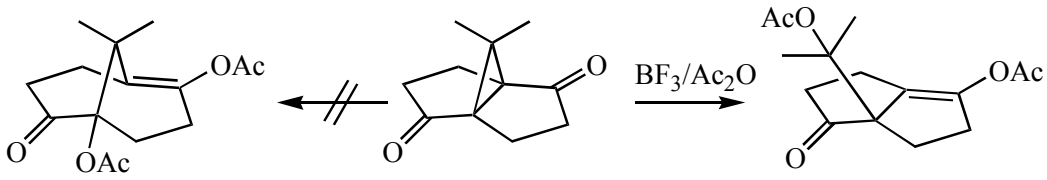


Scheme 29: Rearrangement of the carbocation **92** to the α,β;β,γ-unsaturated endione **78**

3.5.3 Reaction of 84 with borontrifluoride-etherate

Borontrifluoride-etherate ($BF_3 \cdot Et_2O$) was reported[61] to cleavage a cyclopropane being conjugated with a carbonyl group to give an enolacetate. Cyclopropyl diketone **84** was treated with $BF_3 \cdot Et_2O$ at –78 °C under an argon atmosphere (Scheme 30). Unfortunately, the opening proceeded in the same mode of as seen before with acid catalysis to give **96** with a

yield of 62% instead of central bond cleavage. Besides **96**, compound **78** was formed again (15%).

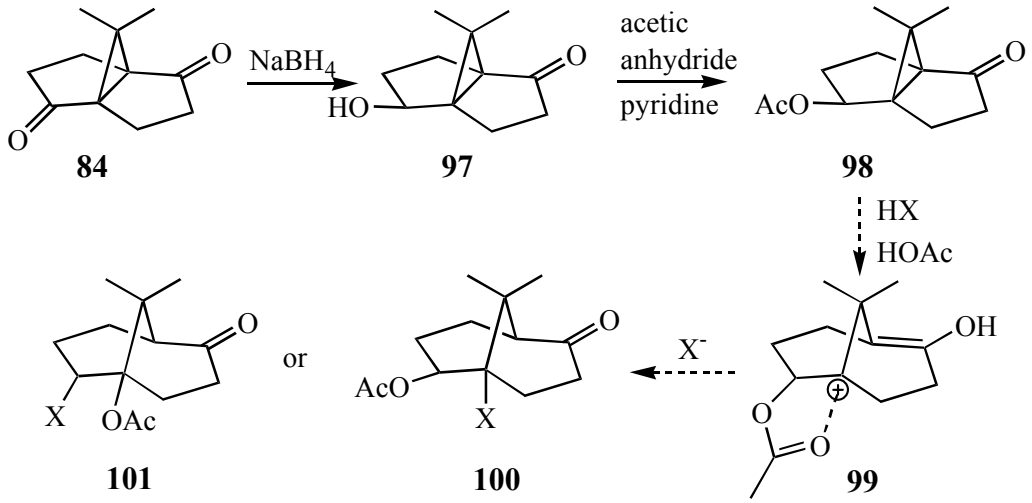


95 **84** **96**

Scheme 30: Borontrifluoride-etherate treatment of the cyclopropyl diketone **84**

3.5.4 Attempt to cleave the central bond of 98 by the aid of anchimeric assistance

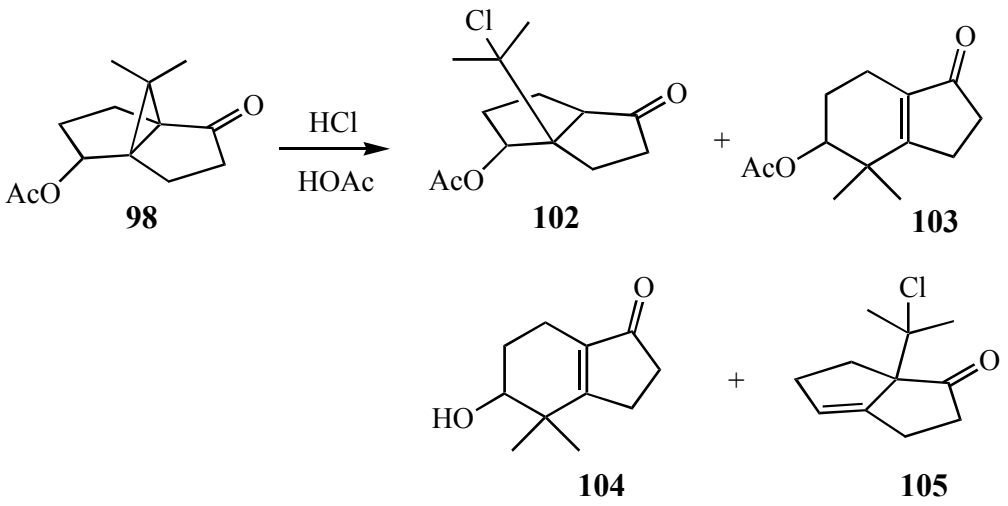
Since the propellane bond in **84** is not sufficiently activated for cleavage as outlined before, we decided to replace one carbonyl by an acetyl function. By this way, the intermediate carbocation is hoped to be stabilized via anchimeric assistance[62] by the acetyl so that cleavage of the central bond might be facilitated. The replacement of a carbonyl with acetyl was achieved in two steps, that are reduction of the carbonyl to the alcohol **97** by $NaBH_4$ and esterification to **98** (Scheme 31).



84 **97** **98** **99** **100** **101**

Scheme 31: Attempt of the cleavage of the central bond in **98** with the aid of anchimeric assistance by the –OAc group in **99**

The ability of oxygen to assist in the intramolecular departure of leaving groups is a classical example of neighboring group participation. The lone pair on oxygen serves as the nucleophile and provides the electrons to form e.g. a Prévost-type intermediate such as **99**. We hoped that the reaction would result with nucleophilic opening of the three-membered ring and **100** and/or **101** would form (Scheme 31). Unfortunately, this attempt resulted in four compounds that were isolated and identified. It is seen that ring cleavage of a the lateral bond of the cyclopropyl ketone took again place and **102** formed as the main product in 27% yield indicating that the reaction follows the same path as with **84**: Lateral cleavage of the cyclopropane and addition of chloride (→ **102**, **105**) or rearrangement of the carbocationic intermediate (→**103**, **104**).

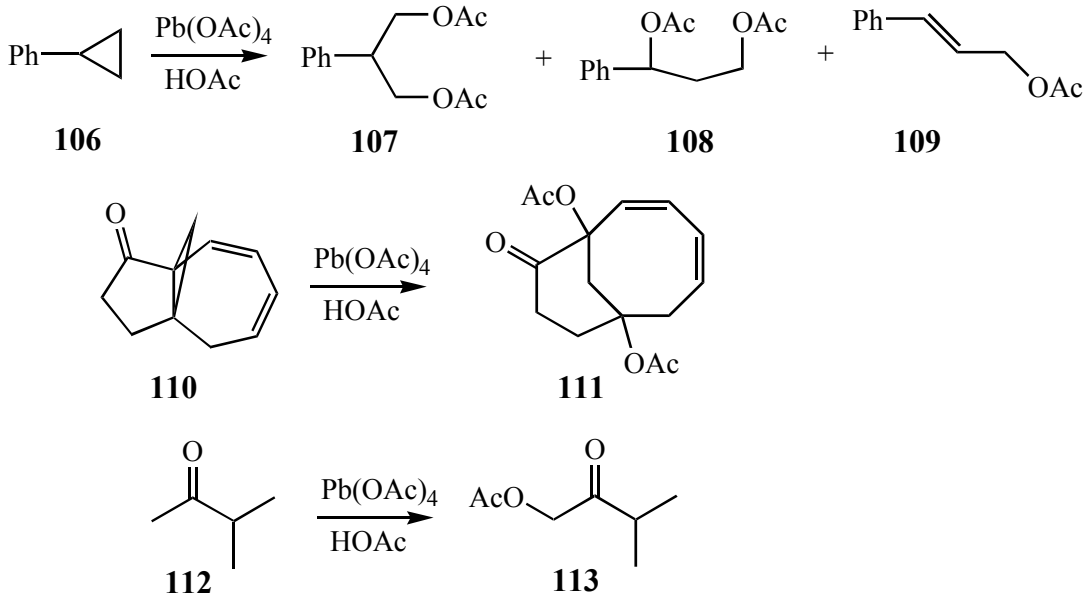


Scheme 32: Reaction of **98** with HCl in HOAc

3.5.5 Treatment of 84 with the lead tetraacetate

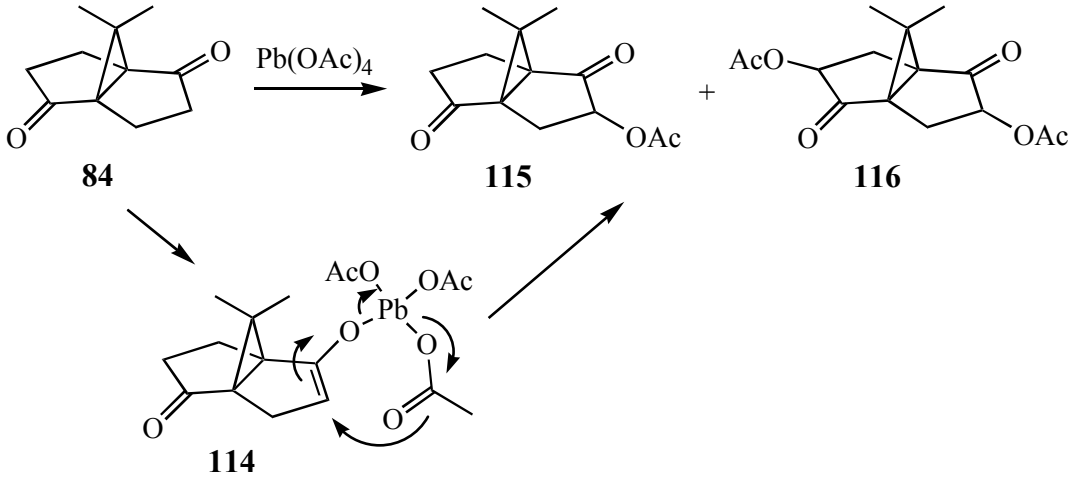
Oxidative cleavage of cyclopropanes by lead tetraacetate ($Pb(OAc)_4$) yields generally diacetates[63a,b] (**107**, **108**, **111**) or mono(un)saturated[62a,64] acetates (**109**, **113**) (Scheme 33). This reaction has been found to be applicable not only for alkyl and aryl cyclopropanes but also for cyclopropyl ketones.[65] On the other hand, it has been reported[64] that the treatment of carbonyl compounds with lead tetraacetate results in α-acetoxy ketones with the preference of less substituted α-carbons and also it was affirmed that enolization of the ketone is a

required intermediate in the formation of acetoxy ketones (Scheme 33). It might be reasonable to expect the formation of bridgehead-substituted or unsaturated bicyclo[3.3.1]nonan-2,6-dione (**85**) derivatives when **84** was reacted with lead tetraacetate (Scheme 34).



Scheme 33: Some examples of opening of cyclopropyl ketones with $Pb(OAc)_4$

Treatment of **84** with $Pb(OAc)_4$ in boiling or ice-cold acetic acid/benzene afforded a major (**115**) and a minor product (**116**) in yields of 53% and 16%, respectively. When the mol ratio of lead tetraacetate was increased to 5, with respect to **84**, **115** was obtained as the major product with a yield of 25% and **116** was the minor product with 8% yield. A plausible mechanism includes displacement of the carbonyl oxygen with acetate ion resulting in the enol intermediate **114** which then rearranges to the products **115** and **116**.



Scheme 34: Reaction mechanism of **84** with the $Pb(OAc)_4$

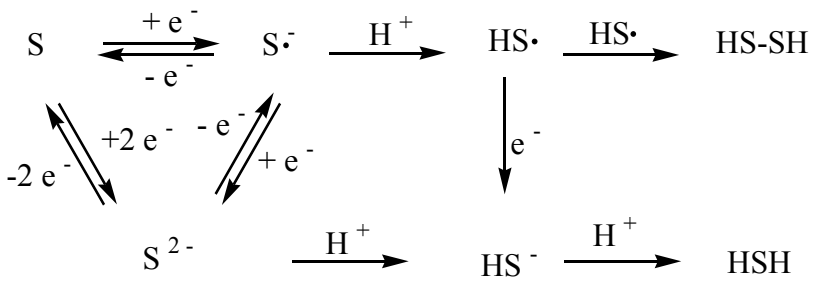
In summary, all attempts that included catalytic hydrogenation, acid-catalyzed reactions including, reactions with borontrifluoride-etherate, acid-catalyzed reactions with neighboring group participation by an acetate and reactions with lead tetraacetate in order to cleave the central carbon-carbon bond of compound **84** failed. There are some reasons for the failure. First of all, the fully substituted cyclopropane such as in compound **84** is stericaly heavily hindered against reagent additions from any side. The cyclopropane is protected from the upper side by the geminal dimethyl groups and from downside by the five-membered rings. In addition to this and as mentioned before, the propellane bond of the cyclopropane to be cleaved is the one that ought to have sufficient conjugation with the π orbitals of carbonyl groups. It must be considered that the lateral bonds fulfill these conditions more satisfactorily than the central bond does.

3.5.6 Dissolving metal reduction

After all these unsuccessful attempts to cleave the central bond in **84**, it was decided to try dissolving metal reduction which are known from literature to reduce α,β-enones as well as cyclopropyl ketones efficiently. However, again sufficient orbital interaction is required between the chromophoric parts of the substrate to be reduced.

One of the earliest reduction procedures is the treatment of such chromophores with active metals either in the presence of a proton donor, which is the reaction medium itself, or followed by treatment with a proton donor.[66] Mostly alkali metals, mainly lithium, sodium, potassium and also zinc, calcium, magnesium are utilized. The dissolving metal reductions include electron transfer from the metal surface or from the metal in solution to the substrate.

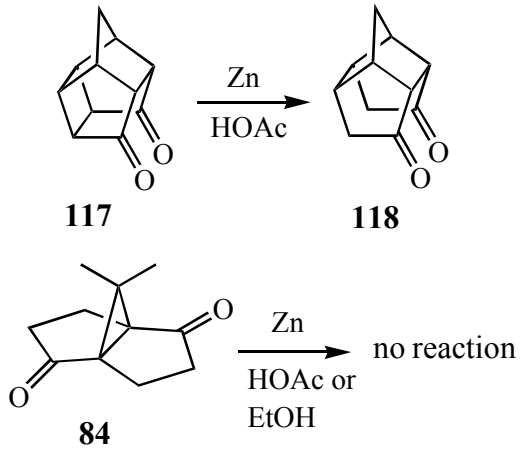
The generally accepted mechanism[66] for dissolving metal reduction of enones involves reversible addition of an electron to a vacant orbital of the substrate (S), yielding a radical anion ($S^{-\cdot}$). The latter can be protonated to give a neutral radical which may either dimerize or accept another electron and a proton. Also, stepwise or simultaneous reversible addition of two electrons to S can give a dianion capable of accepting two protons.



Scheme 35: Reaction mechanism of dissolving metal reduction of an α,β-enone as substrate (S)

3.5.6.1 Treatment of 84 with zinc

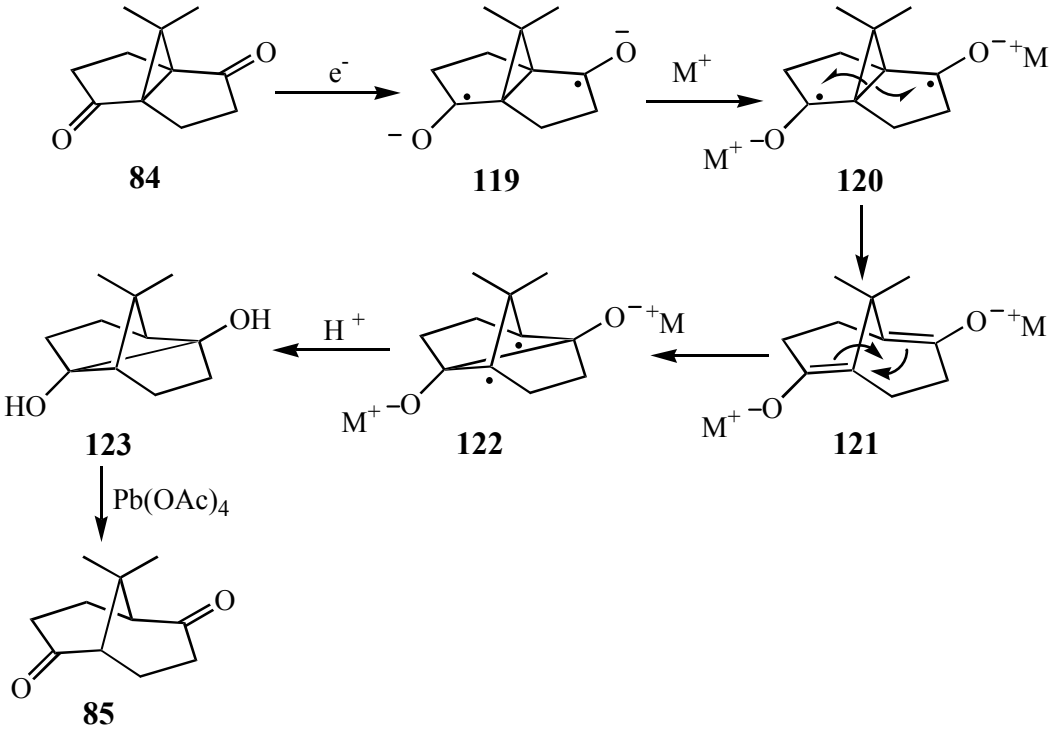
In acetic acid or in ethanol solution of potassium hydroxide, zinc can transfer electrons to the substrate. For example, conjugated 1,4-enedione systems generate[67] a radical dianion which leads to formation of a saturated dione. In addition, treatment of γ-diketones with zinc in acetic acid results[68] in cleavage of the α,β-carbon bond in the four-membered ring. The conversion of **117** to **118** is a good example for such kind of cleavage reactions (Scheme 36). Unfortunately, the reaction of **84** with zinc in acetic acid or with potassium hydroxide in ethanol resulted with complete recovery of the starting material. Moreover, increase of the reaction time and temperature did not change the result.



Scheme 36: Conversion of diketone **117** to **118**

3.5.6.2 *Birch* and *Bouveault-Blanc* reduction of 84

Another type of dissolving metal reductions[69] is the *Birch* reduction[70] (Li or Na in liquid ammonia) and *Bouveault-Blanc* reduction[69] (Li or Na in alcohol). The treatment of **84** with excess lithium in ammonia gave the pinacol 9,9-dimethyltricyclo[3.3.$1^{2,6}$.$0^{1,5}$]non-1,5-diol (**123**) in 60% yield besides a trace of **85** (Scheme 37) which constituted a first but rather limited success in these efforts. Hence, the compound **85** was generated during the reaction. *Bouveault-Blanc* reaction of **84** (Na in ethanol or isopropanol/toluene) led exclusively to the pinacol **123**. By using a large excess of Na with respect to **84**, the reaction yield increased up to 80%. Cleavage of the pinacol **123** was achieved by lead tetraacetate treatment and the target product **85** was synthesized successfully in 55% yield. *Birch* reduction and *Bouveault-Blanc* reduction, both have the same mechanism to crack the cyclopropane conjugated with the carbonyl groups. As it is seen in Scheme 37, the reaction starts with electron transfer and diketyl forms. After the cleavage of the central bond, the intermediate diradical abstracts protons from the solvent and pinacol **123** is produced. Lead tetraacetate is widely used[71] to cleave pinacols and indeed application of this oxidation process to **123** resulted smoothly in the formation of the expected diketone **85** (yield of the overall process **84** → **85**: 44%).



Scheme 37: Reaction mechanism of cleavage of the central bond of **84** by using *Birch* and *Bouveault-Blanc* reactions (→ **123**)

3.5.6.3 Treatment of 84 with potassium-graphite (C_8K)

A further attempt to transform **84** directly to **85** was finally successful by application of the following method of reduction. Potassium-graphite-intercalated compounds[72] into C_8K is widely used as method to reduce organic compounds. Graphite has a lamellar structure and appears in nature in two forms: hexagonal and rhombohedral. The most stable form is hexagonal having a layer stacking sequence of ABABA-- with an interlayer distance of 3.35 Å and the layers are not superimposable. Rhombohedral graphite has a layer sequence of ABCABC-- stacking where every third layer is superimposable. This form exists rarely and it is not used as a host material for the synthesis of graphite-intercalated compounds.

Electronically, graphite is a semimetal[73]. Bonding between carbon atoms involves sp^2-hybridized orbitals. The structure of graphite shows the voids between the planar sp^2-hybridized carbon sheets. Intercalation is achieved by the insertion of ions, atoms or molecules into this space without destruction of the host-layered bonding network. Bond

distance and stacking order may be altered but the carbon layers of the graphite remain undistorted after the intercalation that is, the planar hexagonal structure is preserved.

The graphite is called the host and the ingested compound is called intercalant, which is classified as donor or acceptor according to whether it gives electrons to graphite or abstracts electrons from the host.[72] The known electron donor intercalants are alkali metals including Li, K, Rb, Cs and alkaline earth metals such as Ba, Ca, St as well as transition metals as Eu, Yb. The most widely used electron acceptor intercalants are $FeCl_3$. Br_2, HNO_3, AsF_5.

The stage of intercalation is the ratio of host layer (graphite) to guest layers (potassium).[72] Depending on the conditions of the preparations, the stages may be obtained from 1 to 8. When higher temperature/pressure is applied, higher stages of potassium graphite-intercalation are obtained.[74] Since the carbon hexagons do not superimpose in two neighboring planes in pure graphite, these planes stack in ABAB configuration. In the first stage (C_8K), planes stack in A/A/A configuration and it is the most concentrated one because of highly filled interlayer voids. In the second stage ($C_{24}K$), the stacking sequence is AB/BC/CA/AB and the stacking sequence for the third stage ($C_{36}K$) is ABA/ACA/ABA.[73]

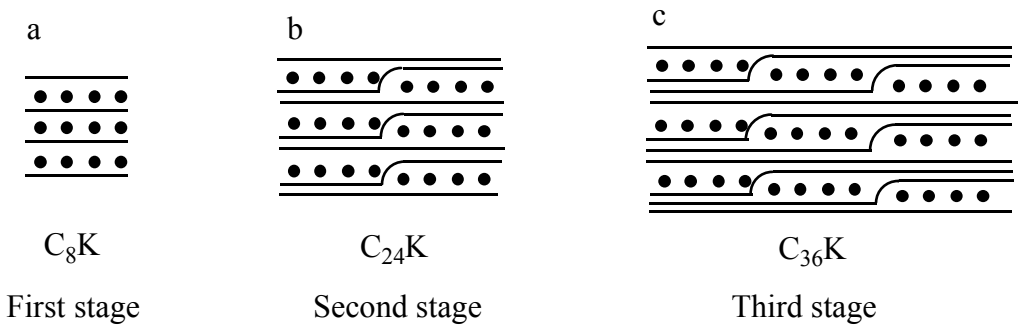


Figure 4: Sequences of carbon (—) and potassium (●) layers :
a) C_8K, b) $C_{24}K$, c) $C_{36}K$

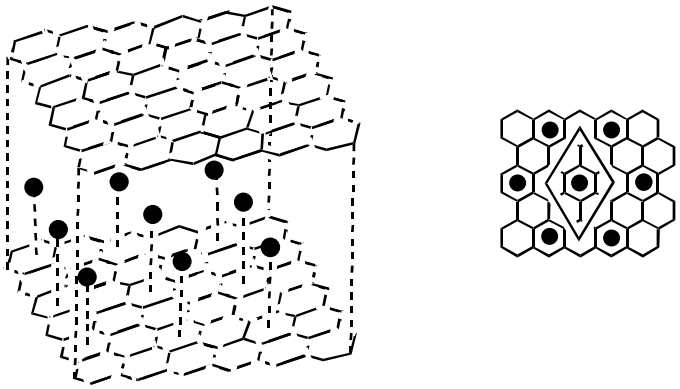
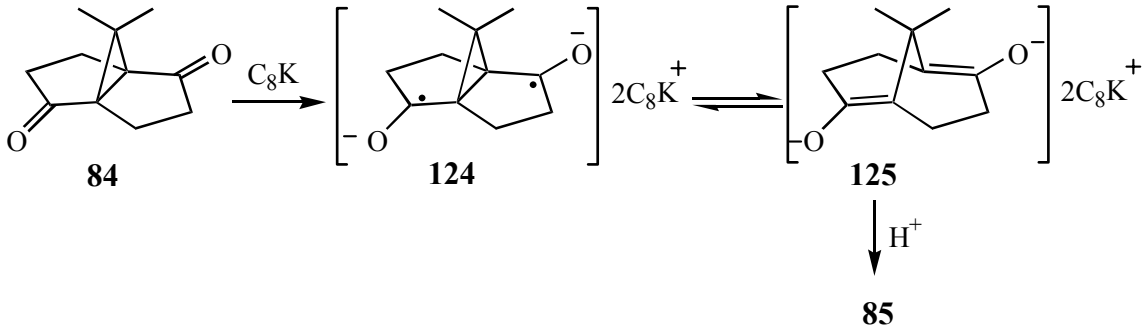


Figure 12: Structure of the C_8K intercalate a) three-dimension view b) unit cell

The presence of potassium atoms in the graphite influences the reactivity of 4s electrons and there is a reversible fast electron transfer from the 4s electrons to the π system of the graphite.[75] The substrate is absorbed at the surface of C_8K and electrons are transferred from the edge of it.[72] Potassium-graphite was used[73] for *Wurtz* reactions, reduction of α,β-unsaturated carbonyls and alkyl halides, hydrogenation, polymerization and reduction of polycyclic hydrocarbons.

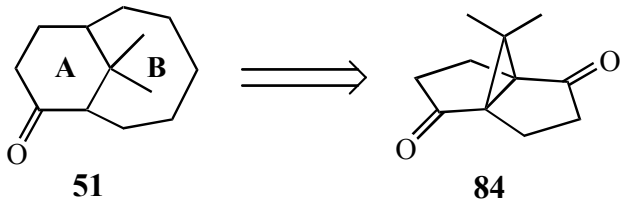
The reducing agent potassium-graphite (C_8K) was applied to compound **84** for the cleavage of the central bond. C_8K was synthesized[76] by adding freshly cut potassium (very important; *note* that old potassium can lead to explosion and fire under the given reaction conditions) to vigorously stirred graphite at 160 ºC under an argon atmosphere. After cooling to room temperature, bronze-colored laminate compound of the intercalation medium C_8K was formed. Addition of the substrate **84** was completed in dry THF via syringe at room temperature. The reaction takes 5-6 days, in case of a shorter reaction time the yield decreases. In addition, treatment with old potassium also decreases the reaction yield. The reduction of **84** must have the same or at least similar mechanism as the *Birch* reduction: The anticipated mechanism for this reaction is outlined in Scheme 38. The initial step involves electron transfer from the edge of the potassium-graphite intercalation material to diketone **84** to generate a dianion radical **124**. Rearrangement of **124** gives the enolate anions via homolytic cleavage of the central bond (→ **125**). By proton abstraction from the solvent, being dry THF, compound **85** is obtained.



Scheme 38: Reaction mechanism of cleavage of the central bond of **84** with potassium-graphite intercalated medium (C_8K)

3.6 Attempts of ring enlargement in 85

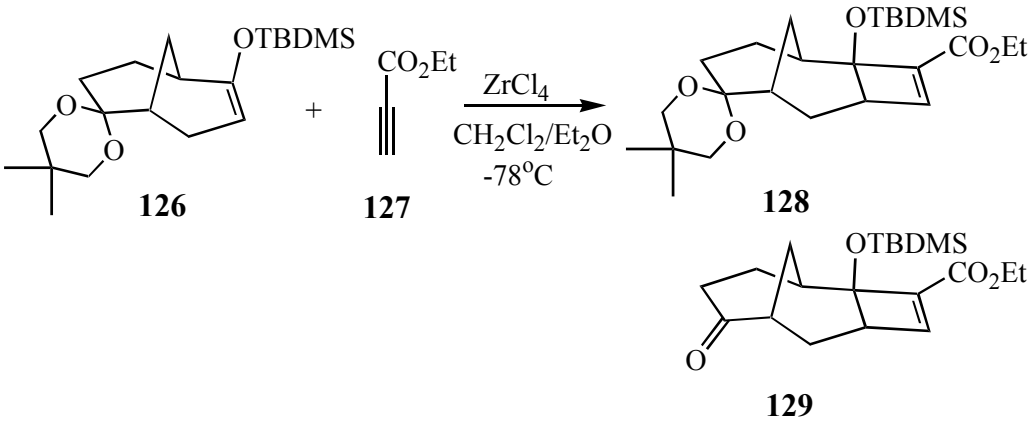
After the cleavage of the central bond of **84**, the next target was to synthesize a compound having a structure like bicyclo[5.3.1]undecene (**51**) which is a potential precursor of the AB-ring part of taxane (Scheme 39).



Scheme 39: AB rings of the skeleton of taxol (**1**)

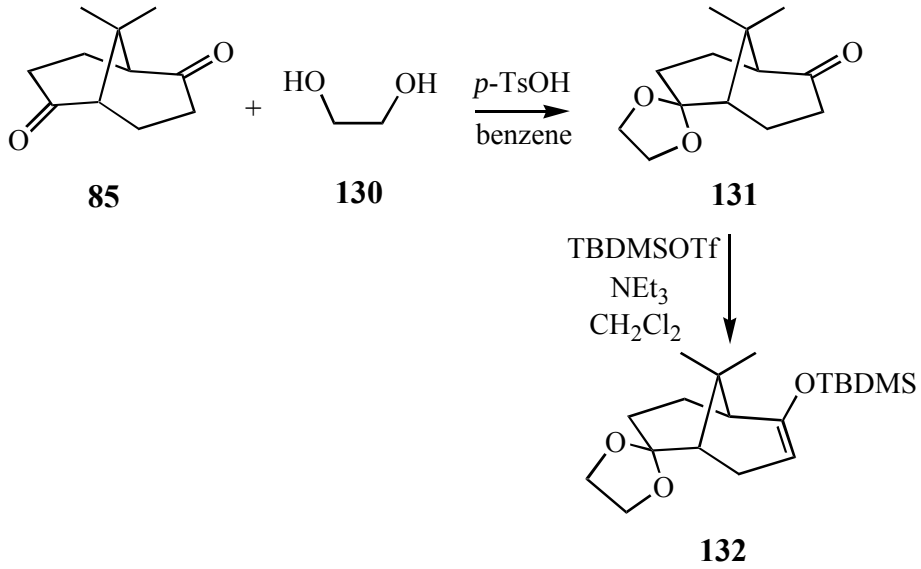
The required ring enlargement can be managed by formation of a cyclobutene, followed by fragmentation of this small ring. It has been reported[77] that $ZrCl_4$-catalyzed [2+2] cycloaddition of ethyl propiolate (**127**) to *tert*-butyldimethylsilyl enol ether **126** results in the cyclobutene esters **128** and **129** (Scheme 40). $ZrCl_4$ was dissolved in the reaction mixture by adding Et_2O to the reaction solvent CH_2Cl_2 in 10:1 ratio. Actually, the catalyst $ZrCl_4$ is not soluble in apolar solvents. Addition of oxygen-containing solvents, like Et_2O or THF,

provides the solubility of the catalyst by coordination to the $ZrCl_4$. In addition, it was noted that when acetyl dicarboxylate was used, no cyclobutene was formed.[77]



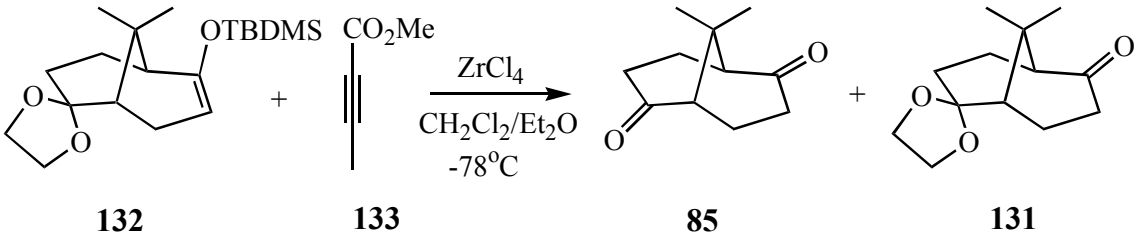
Scheme 40: $ZrCl_4$-catalyzed [2+2] reaction of **126** with ethyl propionate **127**

Since **85** and **126** have similar structures, **85** was converted to the silylenol ether **132** (Scheme 41). For this reason, one of the carbonyls was protected by using 1,2-ethanediol (**130**) as the protecting reagent. The monoprotected compound **131** was obtained[78] with 65% yield in the presence of *p*-toluenesulfonic acid as catalyst by refluxing in a *Dean-Stark* apparatus. After that, ketone **131** was transformed into the *tert*-butyldimethylsilyl enolether **132** in quantitative yield by treatment with *tert*-butyldimethylsilyltriflate (TBDMSOTf).[77]



Scheme 41: Monoprotection of **84** as *tert*-butyldimethylsilyl enol ether **132** via **131**

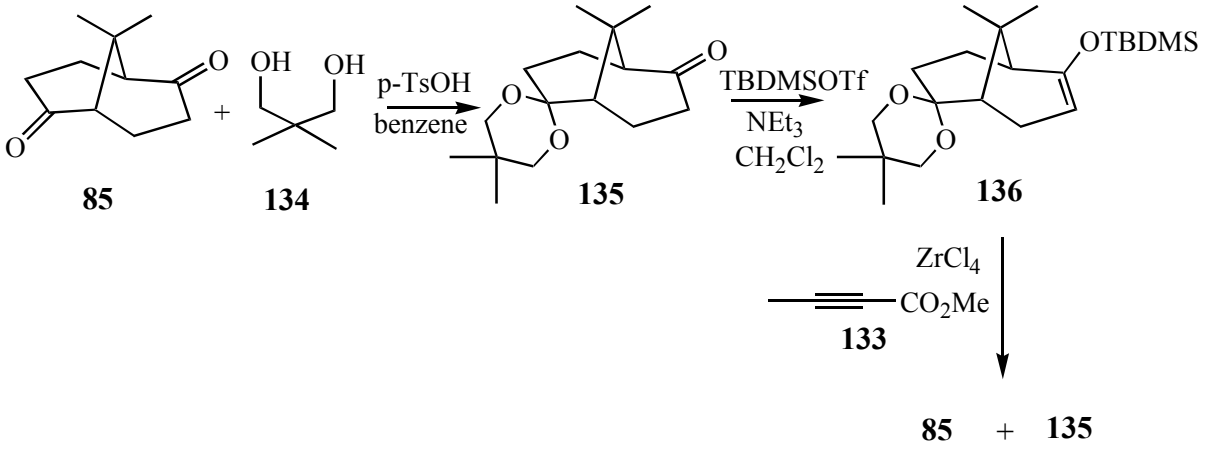
The silylenol ether **132** was then treated with $ZrCl_4$ and methyl but-2-ynoate (**133**) at –78 ºC (Scheme 42). Unfortunately, this attempt of $ZrCl_4$-catalyzed [2+2] reaction[77] of **132** and **133** failed. Compounds **85** and **131** were recovered with 45 and 41% yield, respectively.



132 **133** **85** **131**

Scheme 42: $ZrCl_4$-catalyzed [2+2] reaction of **132** and methyl but-2-ynoate (**133**)

The reason of this failure might be the steric hindrance of the 5-membered protecting group towards the reduction medium. For that reason, another protecting group, 2,2-dimethylpropane-1,3-diol (**134**) which is conformationally more flexible than the previous one, was used[77] (Scheme 43). This protection yielded **135** in 61%. After treatment of **135** with TBDMSOTf in the presence of NEt_3, the enolether **136** was obtained in quantitative yield.

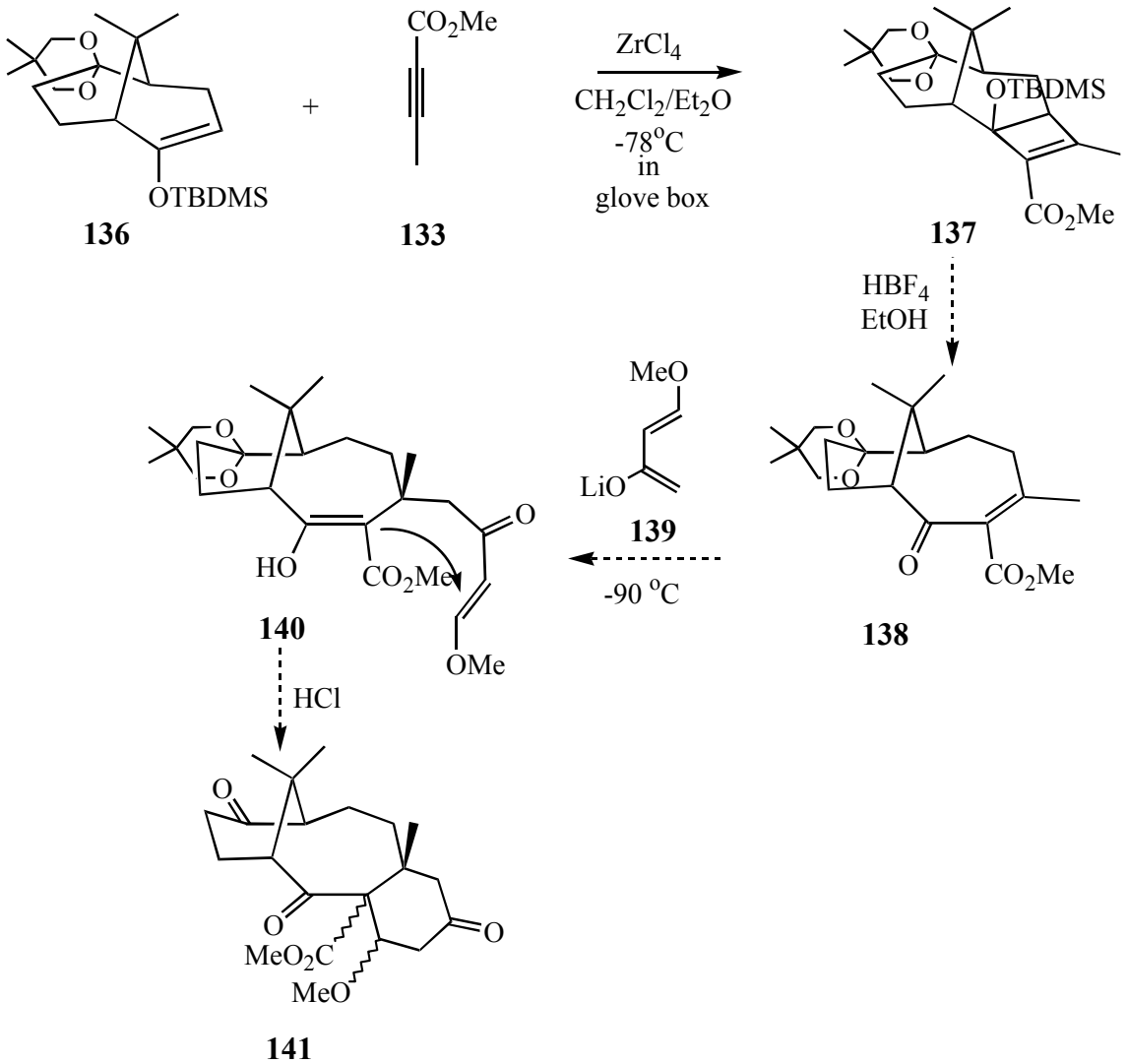


Scheme 43: $ZrCl_4$-catalyzed [2+2] reaction of enolether **136** with **133**

Application of the previously applied procedure to the silylenol ether **136** with methyl but-2-ynoate (**133**) in presence of $ZrCl_4$ gave unfortunately back **85** and **135**. The failure of the $ZrCl_4$-catalyzed [2+2] cycloaddition of **132** and **136** can be explained by the oxophilic character of the catalyst. Since $ZrCl_4$ has not any electron at the d orbitals, it is very oxophilic and interacts with any oxygen-containing compound very easily. If there is even a trace amount of air or water in the reaction medium the catalyst turns to $ZrOCl_2$ and HCl. As a result, the acetal and enolether functions of **132** and **136** reform **85** and the monoprotected diketones **131** and **135**, respectively. Due to the oxophilic character of $ZrCl_4$, the [2+2] cycloaddition of **132** and **136** should be studied in the future under a strictly moisture- and oxygen-free argon atmosphere in a glove box.

4 Outlook

The future prospects of this work consist of mainly two parts: The first part involves the cleavage of central bond of **84** and the ring enlargement which starts with the $ZrCl_4$-catalyzed [2+2] reaction of **136** and but-2-ynoicacid methylester (**133**) in the glove box. As mentioned previously, the oxophilic character of $ZrCl_4$ makes it very sensitive to even trace amounts of water and oxygen. After the synthesis of the [2+2] adduct **137**, the cyclobutene moiety should be rearranged[77] to give **138** by heating **137** with HBF_4 in EtOH. The C ring of the taxol skeleton is planned to be introduced via *Michael* addition[79] (**138** → **140**) and treatment with HCl (→ **141**). The addition of **139** to **138** should preferentially occur from downside (→ **140**).



This addition of **139** to **138** is essential for obtaining the correct ring junction geometry in view of the ABC-ring assembly related to the taxane target structure. In order to be able to predict the outcome of this addition, quantum mechanical calculations (geometry optimization) of **138** were performed.

Geometry optimizations were performed employing density functional theory.[80] The pure BP function was used,[81] in combination with SV(P) basis sets.[82] For all calculations, the TURBOMOLE program[83] package was used and the calculations were performed for vacuum conditions. Furthermore, only charge neutral systems were investigated. The structures were plotted employing gopenmol[84] (Figure 14).

Indeed an addition of **139** on the underside of **138** seems to be sterically less hindered as compared to a top side attack. The geminal dimethyl group is seemingly shielding the latter side efficiently enough. As a result, the correct relative configuration of the C-8 methyl should be obtained.

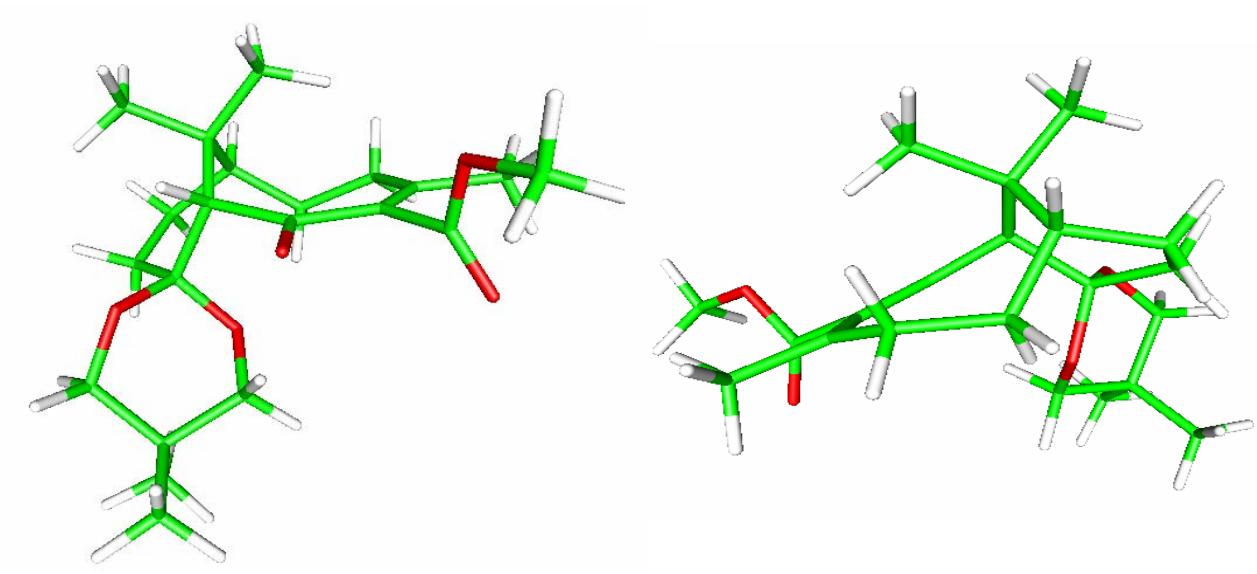
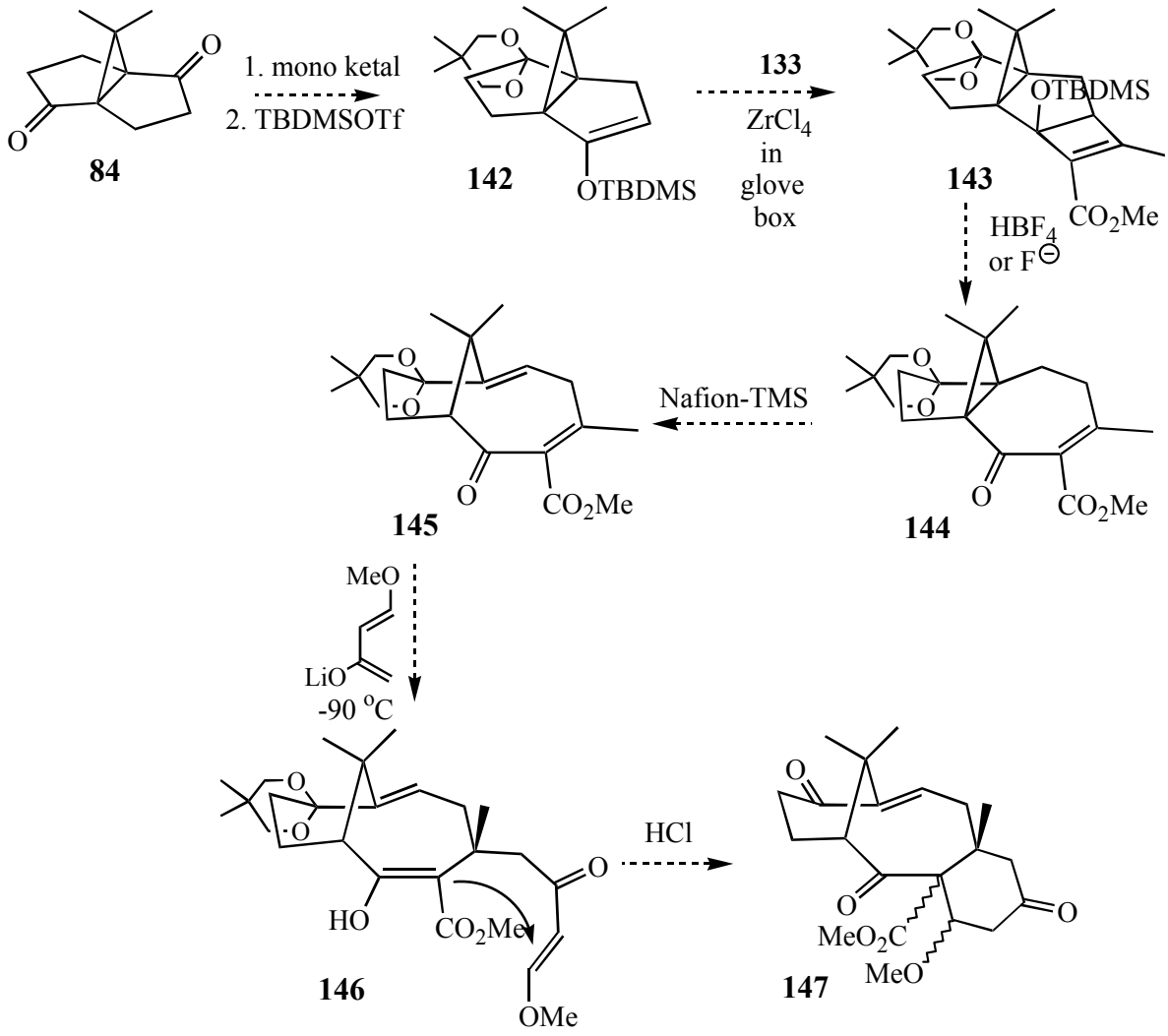


Figure 14: Optimized geometry of **138**. Left: South view, Right: North view. Modelling performed in collaboration with Dr. S. Sinnecker (Max Planck Institute for Bioinorganic Chemistry)

A modification of this future approach could involve first the ring enlargement and then the cleavage of the central bond. For the ring enlargement, the known procedure for the $ZrCl_4$-catalyzed [2+2] cycloaddition reaction will be applied (**142** → **143**). The advantage of this second part is the mild cleavage of the cyclopropane and the introduction of a bridgehead double bond (**144** → **145**) which will allow further functionalizations. **144** will be treated with Nafion-TMS[85] for the cyclopropane opening including the elimination step. The C ring of the taxol skeleton will be introduced via *Michael* addition[79] (→ **146**) and treatment with HCl (→ **147**), a reaction sequence which was described before. The stereochemical outcome of this sequences should be analogous to the one described for **138** → **140** → **141**.



Another geometry optimization has been performed for the compound **145**. As mentioned before, the relative configuration of the methyl at C-8 is important. In order to provide that *Michael* addition (**145** → **146**) will be achieved on the underside of **145** the geometry optimization, which was studied for **138**, was performed also for **145**. The result of density functional theory (Figure 15) shows that dienolate **139** again add to **145** on the underside because of more steric interactions to be expected on the top side.

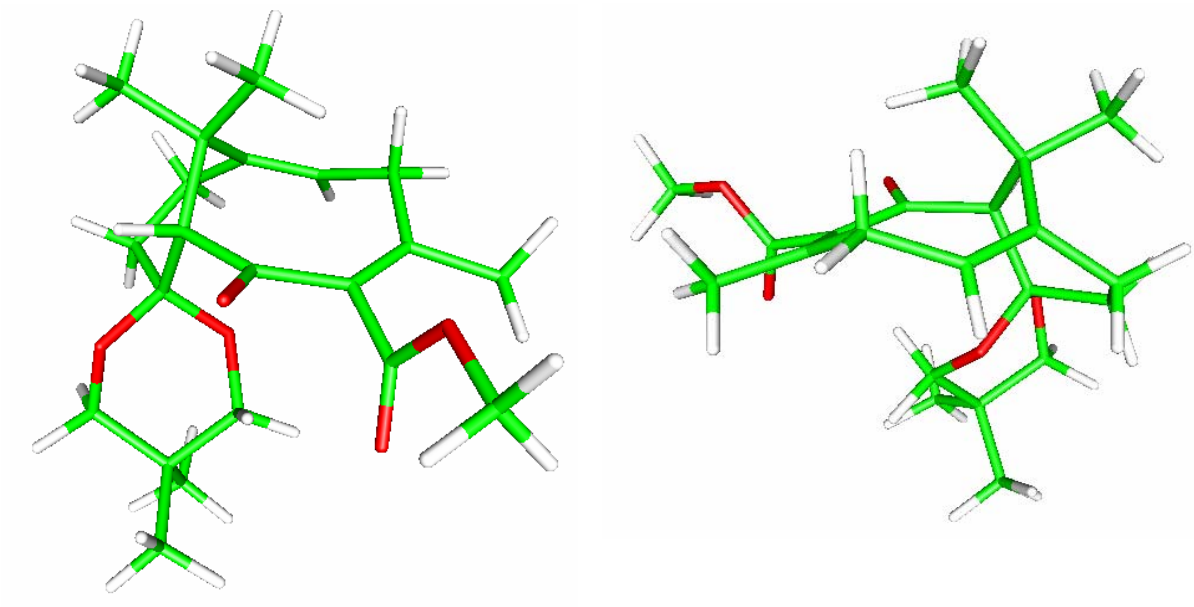
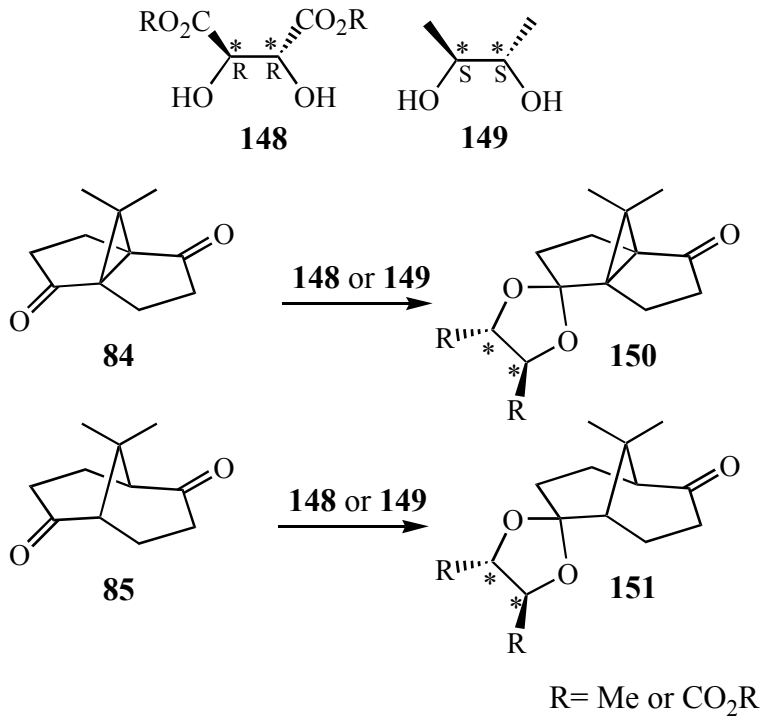


Figure 15: Optimized geometry of **145** Left: South view, Right: North view. Modelling performed in collaboration with Dr. S. Sinnecker (Max Planck Institute for Bioinorganic Chemistry)

A last but important point should concern studies regarding the introduction of chirality into our synthetic approach. A likely solution could involve the monoacetalization step on **84** or **85** using a C_2-symmetrical reagent like optically active tartrate (**148**) or butane-2,3-diol (**149**) to give e.g. **150** as chiral building block.



5 Experimental section

I would like to thank to following co-workers of the Max Planck Institute for Bioinorganic Chemistry and the Max Planck Institute for Coal Research for their most valuable services: Mrs. K. Sand and Mr. J. Bitter (NMR spectra); Mr. W. Schmoeller and Mr. W. Joppek (MS spectra). My appreciation is also extended to all the members of the administration, library staff and technical staff of the Max Planck Institute for Bioinorganic Chemistry, whose assistance has made the completion of this work both possible and enjoyable.

I would like to thank to Dr. Sebastian Sinnecker of our institute especially for the DFT calculations and geometry optimizations.

5.1 Instruments, methods and materials

Melting points (Mp):
Determined on a *Reichert* or *Kofler* apparatus and are uncorrected.

Ultraviolet absorption spectra (UV):
Recorded with either a *Carry 17* or *Bruins Omega-10* spectrometer. λ_{max} values are given in nm; ε values in parantheses.

Infrared spectra (IR):
Recorded with KBr-pressed plates using *Brucker IFS 66* (FT-IR-Spectrometer) or a *Perkin-Elmer 1600* instrument. Frequency values are given in cm^{-1}. The symbols s (strong), m (medium) and w (weak) characterize the relative band intensities.

Mass spectra (MS):
Recorded on *Finnigan MAT 311A* or *MAT 95* (HRMS) instruments at 70 eV ionization energy. Data are presented in m/z values. When required, molecular ion peaks were ascertained by chemical ionisation (CI) or fast atom bombardment (FAB) techniques.

Nuclear Magnetic Resonance spectra (NMR):

Recorded in *Fourier* Transform mode on the following *Brucker* instruments: An ARX-250 (250 MHz for ^{1}H, 63 MHz for ^{13}C), an AM-400 (400 MHz for ^{1}H, 100.6 MHz for ^{13}C) and a DRX-500 (500 MHz for ^{1}H, 125.8 MHz for ^{13}C) with dilute solutions in deuteriochloroform ($CDCl_3$) at 300 K unless stated otherwise. The chemical shift values are given in δ units (ppm, parts per million) with trimethyl silane as internal standard. All coupling constants, *J*, are reported in Hz. The multiplicity of a signal is designated by one of the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad).

Thin layer chromatography (TLC):

Performed on 0.20 mm (aluminium) silica gel plates (F_{254}, *Merck*). As developing reagent, a solution containing 30 g vanillin, 5 ml conc. H_2SO_4 and 1000 ml EtOH. The plates were visualized with UV light and then thermally developed.

Column chromatography:

Gravimetric columns or high pressure variants on self-packed *Kronlab Sepakron-FPGC* glass columns of different sizes on Merck silica gel 60 (0.063-0.20 mm or 0.04-0.063 mm) with pressure pump *Buechi 688* or *Besta E-100* and pressure 1-10 bar were used; all solvents were distilled before use.

Irradiation:

All samples were stirred and flushed with argon prior to use. Cylindrical *Pyrex* reaction vessels, equipped with cooling fingers (H_2O coolant), were used. *Rayonet* reactors (RPR-208-System, Southern New England Ultraviolet company) with sixteen 350 nm (λ_{max}) lamps (24 watt/lamps) were employed for irradiation.

Solvents:

Purchased from *Merck*, *Aldrich* or *Fluka* and used directly or purified by standard procedures. Absolute solvents were purchased from *Fluka* and kept on molecular sieves.

Reagents: The chemical name, abbreviated molecular formula (with parantheses, if appropriate), quality, purification procedure and company of purchase are listed below.

Acetic acid (HOAc): z.S., *Merck*

Acetic anhydride: 95%, *Merck*

Acetophenone: 99%, *Fluka*

Amberlyst 15: 99%, *Fluka*

2,2'-Azobisisobutyronitrile (AIBN): 98 %, *Aldrich*

n-Butyl lithium (n-BuLi): 1.6 M in *n*-hexane, *Fluka*

Boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$): BF_3 content of 46.5-49.5%, *Fluka*

But-2-ynoate : 99%, *Acros*

Chromium (VI) oxide (CrO_3): 99%, *Fluka*

1,3-Cyclohexadione 97%, *Fluka*

1,2-Ethanediol: 99%, *Merck*

Graphite: 99%, *Fluka*

Methyl iodide (CH_3I): 99%, *Fluka*

Lead tetraacetate ($Pb(OAc)_4$): 95%, *Fluka*

Lithium (Li): 99%, *Fluka*

10% Pd-Charcoal: 99%, *Fluka*

Polyphosphoric acid: 84%, *Fluka*

Potassium (K): 99%, *Fluka*

Potassium carbonate ($K_2CO_{3)}$: 99%, *Fluka*

Propargyl alcohol: 99%, *Fluka*

Propylic acid: 96%, *Across*

Pyridine: 99%, *Fluka*

5% Pt-Charcoal: 99%, *Fluka*

Sodium (Na): 99%, *Fluka*

Sodium hydrogencarbonate ($NaHCO_3$): 99%, *Merck*

Sodium boronhydride ($NaBH_4$): 96%, *Aldrich*

Sulphuric acid (H_2SO_4): z.S., *Merck*

tert-Butyldimethylsilyltriflate (TBDMSOTf): 98%, *Aldrich*

Triethylamine (NEt_3): 99%, *Merck*

Tri-*n*-butyltin hydride (Bu_3SnH): 97%, *Aldrich*

Toluene-*p*- sulphonic acid monohydrate (PTSA): 98%, *Fluka*

Zirconium tetrachloride ($ZrCl_4$): 99%, A*ldrich*

5.2 Nomenclature and general synthetic and photochemical procedures

Nomenclature: Compounds have been named according to the standard nomenclature rules (IUPAC) by means of the program *AUTONOM*, with the exception that the numbering system has in some cases been chosen more conveniently with respect to NMR signal assignments.

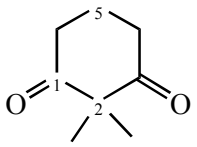
General synthetic procedures: A cold bath of –78 °C was prepared from a mixture of acetone and dry ice. Oxygen or moisture sensitive reactions were performed under an argon flow in either oven- or heat-gun-dried glassware equipped with rubber septa. Air or moisture sensitive liquids or solutions were transferred through a funnel under a rapid argon flow. "Concentration" involved drying of the combined organic layers over anhydrous Na_2SO_4, filtration and solvent removal by roto-evaporation and high vacuum (10^{-1}-10^{-3} torr). "Chromatography" refers to column separation technique performed on *Merck* silica gel 60 (0.063-0.20 mm; 100 fold), unless stated otherwise, giving product purities of >97%.

5.3 Reactions

5.3.1 Synthesis of 56

To a stirred solution of 1,3-cyclohexandione (**55**) (25 g, 0.223 mol) and acetone (200 ml) was added anhydrous K_2CO_3 (90 g, 0.70 mol) at 50 ºC. The reaction mixture was refluxed for 15 hours and then cooled to room temperature. Afterwards the resulting mixture was filtered and the filtrate was concentrated. Chromatography of the crude product on a flash column of silica gel with pentane-ether (1:1) gave 2,2-dimethylcyclohexane-1,3-dione (**56**) with 55% yield (23.9 g).

2,2-Dimethylcyclohexane-1,3-dione (56):



MS (EI; m/z, rel. int.):
140 (49.37, M^+, $C_8H_{12}O_2$), 97 (100), 70 (83), 67 (37), 55 (70), 42 (79), 41 (48).

HRMS (EI; m/z):
calculated for $C_8H_{12}O_2$: 140.083730; found: 140.083877.

^{1}H NMR (250 MHz): 2.64 (t, J=6.66 Hz, 4H); 1.9 (m, 2H); 1.26 (s, 6H).

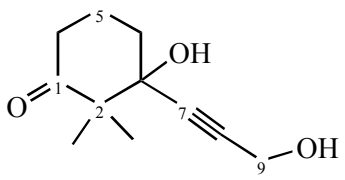
^{13}C NMR (63 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):
210.28 (Cq, C-1,3); 61.55 (Cq, C-2); 37.18 (CH_2, C-4,6); 22.05 (CH_3, C-7,8); 17.86 (CH_2, C-5).

IR (KBr):
2966w, 2941w, 1727m, 1695m, 1383m

5.3.2 Synthesis of 3-Hydroxy-3-(3-hydroxy-prop-1-ynyl)-2,2-dimethyl-cyclohexanone (57)

A solution of propargylalcohol (95%, *Fluka*, 1,40 g, 25 mmol) in 140 ml dry THF was cooled to –78 °C under stirring and argon atmosphere. To this solution was added dropwise 34.4 ml (55 mmol) of an *n*-BuLi solution (1.6 M in hexane, *Aldrich*) during 20 min. The resulting mixture was stirred for further 2 hours, then a solution of 2,2-dimethylcyclohexan-1,3-dione (**56**, 2.8 g, 20 mmol) in dry THF (20 ml) was added dropwise, before stirring for further 8 hours. 100 ml of water was then added and the mixture slowly warmed to room temperature. The organic phase was separated and the aqueous phase extracted with ether followed by drying of the combined organic layers over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a flash column of silica gel with pentane-ether (1:1) to give product **57** 2.04 g (54%) as a white solid.

3-Hydroxy-3-(3-hydroxy-prop-1-ynyl)-2,2-dimethyl-cyclohexanone (57):



MS (EI; m/z, rel. int.):
196 (8.2, M^+, $C_{11}H_{16}O_3$), 178 (6), 163 (28), 150 (9), 135 (18), 122 (13), 111 (36), 98 (100), 93 (16), 86 (41), 83 (19), 70 (21), 65 (31), 55 (37), 41 (38).

HRMS (EI; m/z):

calculated for $C_{11}H_{16}O_3$: 196.109945; found: 196.109824.

^{1}H NMR (400 MHz):

4.15 (s, 2H, H_2C-9); 4.1 (br. s, 1H, HOC-9); 3.87 (s, 1H, HOC-3); 2.35-2.23 (br. m, 2H); 2.08-1.71 (br. m, 4H); 1.14 (s, 3H, CH_3); 1.08 (s, 3H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):

214.26 (Cq, C-1); 85.84 (Cq, C-7); 83.86 (Cq, C-8); 75.28 (Cq, C-3); 53.53 (Cq, C-2); 50.12 (CH_2, C-9); 36.20 (CH_2, C-2); 33.99 (CH_2, C-4); 22.17 (CH_3); 19.93 (CH_2, C-5); 19.07 (CH_3).

Mp 42.0-44.0 °C.

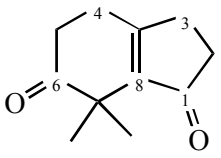
IR (KBr):

3588m, 3499w, 3303s (br.), 1698s, 1468w, 1451w, 1426w, 1383w, 1365w, 1349w, 1176w, 1127m, 1018s, 991w, 960m.

5.3.3 Synthesis of 7,7-Dimethyl-3,4,5,7-tetrahydro-2H-indene-1,6-dione (58)

57 (2.02 g, 10.3 mol) was dissolved in 10 ml acetic acid and 1.01 g amberlyst 15 (*Acros*) added to this solution, then stirred at 95 °C for 20 hours.The amberlyst 15 was filtered off and the filtrate distilled in vacuo to remove acetic acid before the residue was dissolved in ethylacetate, washed with a saturated solution of sodium hydrogencarbonate and the organic phase was thereafter concentrated in vacuo and the residue chromatographed on silica gel with pentan-ether (1:2). The product **58** was obtained as a dark yellow solid in 13.6% yield (0,25 g).

7,7-Dimethyl-3,4,5,7-tetrahydro-2H-indene-1,6-dione (58):



HRMS (EI; m/z):
calculated for $C_{11}H_{14}O_2$: 178.099553; found: 178.099381.

MS (EI; m/z, rel. int.):
178 (95, M^+, $C_{11}H_{14}O_2$), 150 (33), 136 (100), 135 (74), 121 (53), 107 (16), 93 (43), 91 (24), 79 (21), 77 (21).

^{1}H NMR (250 MHz):
2.69-2.61 (m, 4H, CH_2); 2.53-2.43 (m, 4H, CH_2); 1.33 (s, 6H, CH_3).

^{13}C NMR (63 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):
213.56 (Cq, C-6); 207.15 (Cq, C-1); 169.72 (Cq, C-7); 143.92 (Cq, C-9); 44.34 (Cq, C-7); 36.20 (CH_2); 34.61 (CH_2); 28.92 (CH_2); 27.94, (CH_2); 22.86 (CH_3, C-10, 11).

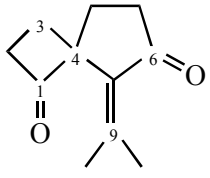
Mp 75-76 °C.

IR (KBr):
3465m (br.), 2956s, 2869w, 1740s, 1720m, 1643s.

5.3.4 Photochemical reaction of 7,7-Dimethyl-3,4,5,7-tetrahydro-2H-indene-1,6-dione (58) (→ 77)

In a cylindrical *Pyrex* irradiation vessel, equipped with a cooling finger, **58** (88.5 mg, 0.497 mmol) was dissolved in 140 ml acetonitrile and degassed under stirring for 1 hour before irradiation at room temperature for 40 hours. The reaction mixture was irradiated in a photochemical chamber reactor (type *Rayonet* RPR-208), equipped with 8 lamps (each 24 W, RUL 350 nm, λ_{max} = 350 nm, emission range 300-400nm). After evaporation of the solvent, the residue was chromatographed on silica gel with pentane-ether (1:2) to give the product **77** (55.1 mg, 62.3%) as a colorless oil besides a second fraction of 14.4 mg (16.3%) of **58**.

5-Isopropylidene-spiro[3.4]octane-1,6-dione (77):



MS (EI; m/z, rel. int.):
178 (22, M^+, $C_{11}H_{14}O_2$), 150 (96), 136 (100), 135 (82), 121 (95), 107 (24), 93 (83), 91 (39), 80 (32), 79 (49), 77 (33), 39 (23).

HRMS (EI; m/z):
calculated for $C_{11}H_{14}O_2$: 178.099380; found: 178.099614.

^{1}H NMR (400 MHz):
3.22-3.08 (m, 2H, CH_2); 2.22 (s, 3H, CH_3); 2.40-2.05 (m, 6H); 1.77 (s, 3H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):
212.43 (Cq, C-1); 204.82 (Cq, C-6); 152.51 (Cq, C-9); 133.05 (Cq, C-5); 70.90 (Cq, C-4); 42.97 (CH_2); 37.70 (CH_2); 32.04 (CH_2); 26.52 (CH_2); 25.86 (CH_3); 21.62 (CH_3).

IR (KBr):
3448s (br.), 2961w, 1776s, 1707s, 1619m, 1437w, 1276w, 1194w, 1112w, 1072w.

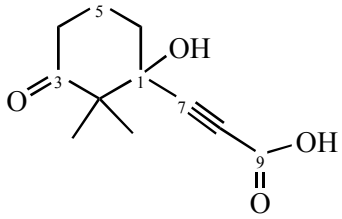
5.3.5 Synthesis of (1-hydroxy-2,2-dimethyl-3-oxo-cyclohexyl)-propynoic acid (54) from either 57 (a) or directly from 56 (b)

(a) To a solution of 1.91 g (9.73 mmol) of **57** in 16 ml acetone was added dropwise a solution of J*ones* reagent (mixture of CrO_3 (1.946 g, 19.46 mmol), 10 ml water and 1.56 ml 97-98% H_2SO_4) at 0 °C (ice bath) during 8 hours, then stirred for further 5 hours, extracted with ether and the combined organic layers washed with brine and dried over sodium sulfate. After the evaporation of the solvent, the crude product was chromatographed on silica gel with pentane/ether/acetic acid (1:1:0.1) to give the product **54** in white crystalline form (1.32 g, 64.5%) and **56** (0.25 g, 18.4%).

(b) To a solution of 1.47 g (20 mmol) propylic acid (96%, *Across*) in 100 ml dry THF were added 16 ml (40 mmol) *n*-BuLi solution (2.5 M in *n*-hexane) dropwise under argon and stirring at –78 °C, followed by stirring of the resulting solution at the same temperature for

another 2 hours. Afterwards a solution of **56** (2.8 g, 20 mmol) in 20 ml dry THF was added dropwise and the mixture was stirred still at the same temperature for 7 days (monitoring of the reaction by TLC). 100 ml of water were then added slowly by allowing the reaction mixture to warm to room temperature. The organic phase was separated and the water layer acidified with dilute HCl and extracted with ethyl acetate. After the combined organic layers were dried over anhydrous Na_2SO_4, and the solvent evaporated at reduced pressure in order to concentrate the crude product which was purified on silica gel with pentane:ether:acetic acid (1:1:0.1) to give **54** in 59% yield (2.47 g).

(1-Hydroxy-2,2-dimethyl-3-oxo-cyclohexyl)-propynoic acid (54):



MS (EI; m/z, rel. int.):
210 (21, M^+, $C_{11}H_{14}O_4$), 192 (10), 166 (13), 150 (26), 149 (22), 105 (16), 98 (100), 91 (22), 86 (20), 85 (52), 70 (24), 67 (58), 55 (37), 53 (33), 43 (39), 42 (37), 41 (54), 39 (31).

HRMS (EI; m/z):
calculated for $C_{11}H_{14}O_4$: 210.089208; found: 210.089249.

^{1}H NMR (400 MHz, CD_3OD):
5.19 (br.s, 1H, HOC-9); 2.60-1.85 (m, 6H); 1.29 (s, 3H, CH_3); 1.23 (s, 3H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY, CD_3OD):
213.81 (Cq, C-3); 154.78 (Cq, C-9); 87.55 (Cq, C-7); 74.79 (Cq, C-8); 53.02 (Cq, C-2); 36.10 (CH_2, C-4); 33.40 (CH_2, C-6); 22.35 (CH_2, C-5); 19.65 (CH_3); 18.65 (CH_3).

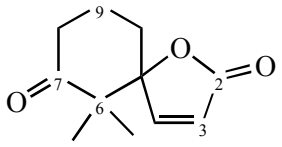
Mp 153-155 °C.

IR (KBr):
3489s, 2957s, 2605s, 2246m, 1707s, 1678s, 1470m, 1425m, 1368s, 1244s.

5.3.6 Synthesis of 6,6-dimethyl-1-oxa-spiro[4.5]decane-2,7-dione (83)

Carboxylic acid **54** (4.1 g, 0.19 mmol) was dissolved in 50 ml ethyl acetate and 10% Pd-charcoal (0.15 g) was added in a two-necked flask which was connected to water pump and hydrogen-filled balloon. This mixture was evacuated at water pump pressure until evolution of bubbles then the valve of the hydrogen-filled balloon was opened. This process was repeated for several times. Then the reaction was left to react under hydrogen and was monitored by TLC. After completion, the catalyst was filtered off and the filtrate washed with saturated sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate. After evaporation of the solvent at reduced pressure, the crude product was chromatographed on silica gel with pentane-ether (1:1) and spiro lactone **83** (2.65 g, 67.6%) was obtained as a white crystalline material. If the reaction time is shortened, the unsaturated analog **82** is synthesized besides the spiro lactone **83**.

6,6-Dimethyl-1-oxa-spiro[4.5]dec-3-ene-2,7-dione (82):



MS (EI; m/z, rel. int.):
194 (41, M^+, $C_{11}H_{14}O_3$), 179 (18), 138 (14), 123 (19), 110 (100), 96 (35), 85 (160), 82 (14), 70 (17), 67 (65), 55 (27), 54 (19), 53 (16), 43 (21), 42 (28), 41 (55), 39 (33). 27 (22).

HRMS (EI; m/z):
calculated for $C_{11}H_{14}O_3$: 194.094295; found:194.094013.

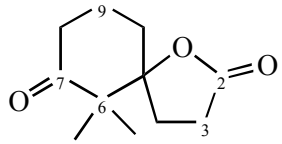
^{1}H NMR (400 MHz):
7.40 (d, 1H, J=5.8Hz); 6.11 (d, 1H, J=5.8Hz); 2.57-2.53 (2H, m), 2.24, 2.10 (2H, m); 1.95-1.85 (2H, m); 1.17 (s, CH_3); 1.06 (s, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):
210.59 (Cq, C-7); 171.41 (Cq, C-2); 156.08 (CH. C-4); 122.27 (CH, C-3); 94.33 (Cq, C-5); 51.01 (Cq, C-6); 36.38 (CH_2); 31.08 (CH_2); 22.22 (CH_3); 20.91 (CH_2); 18.66 (CH_3).

Mp 85-87 °C.

IR (KBr):
2926m, 1752s, 1712s, 1460m, 1384m, 1149m, 1090w, 964s, 914m, 814s.

6,6-Dimethyl-1-oxa-spiro[4.5]
decane-2,7-dione (83):



MS (EI; m/z, rel. int.):
196 (57, M^+, $C_{11}H_{16}O_3$), 178 (5), 168 (12), 126 (15), 111 (100), 98 (17), 83 (15), 70 (14), 55 (33), 42 (21), 41 (28).

HRMS (EI; m/z):
calculated for $C_{11}H_{16}O_3$: 196.109945; found:196.110156

^{1}H NMR (400 MHz):
2.8-2.4 (m, 4H, CH_2); 2.25-2.20 (m, 1H, CH_2); 2.05-1.76 (m, 5H, CH_2); 1.14 (s, CH_3); 1.12 (s; CH_3).

^{13}C NMR (^{13}C-COSY):
211.45 (Cq, C-7); 175.77 (Cq, C-2); 91.95 (Cq, C-5); 52.74 (Cq, C-5); 36.37 (CH_2, C-8); 33.07 (CH_2); 28.55 (CH_2); 28.45 (CH_2); 21.44 (CH_3); 19.69 (CH_2); 18.09 (CH_3).

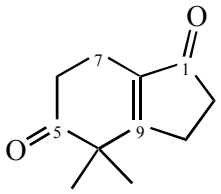
Mp 97-99 °C.

IR (KBr):
2952m, 1772s, 1706s, 1472m, 1388m, 1273m, 1232m, 1208s, 1179m, 1158s, 956s.

5.3.7 Synthesis of 4,4-Dimethyl-2,3,6,7-tetrahydro-4*H*-indene-1,5-dione (78)

Compound **83** (673 mg, 3.4 mmol) and polyphosphoric acid (75 ml) were heated at 90 °C under stirring and argon for 50 hours, then the viscous brown mixture was poured on ice, extracted with ethyl acetate and dried over anhydrous sodium sulfate. After evaporation of the solvent at reduced pressure, the residue was chromatographed on a silica gel column with pentane-ether (1:1) to give **78** as dark yellow crystals (359 mg, 58.7%).

4,4-Dimethyl-2,3,6,7-tetrahydro -4H-indene-1,5-dione (78):



MS (EI; m/z, rel. int.):
178 (100, M^+, $C_{11}H_{14}O_2$), 136 (71), 135 (46), 121 (24), 93 (28), 91 (11), 79 (11).

HRMS (EI; m/z):
calculated for $C_{11}H_{14}O_2$: 178.099380; found: 178.099348

^{1}H NMR (400 MHz):
2.60-2.50 (m, 6H, CH_2); 2.47-2.45 (m, 2H, CH_2); 1.29 (s, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):
212.83 (Cq; C-5); 207.35 (Cq, C-1); 177.03 (Cq, C-9); 136.48 (Cq, C-8); 47.25 (Cq, C-4); 34.74 (CH_2, C-6); 34.72 (CH_2, C-2); 24.72 (CH_2, C-7); 23.66 (CH_3, C-10,11); 19.32 (CH_2).

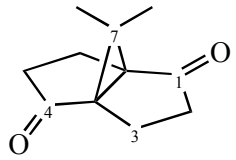
Mp 56-58 °C.

IR (KBr):
3456w, 2970w, 2935w, 1772w, 1735m, 1699s, 1645m, 1447w, 1390w, 1353m, 1231w, 1175m.

5.3.8 Synthesis of 7,7-Dimethyl-tetrahydro-3a,6a-methano-pentalene-1,4-dione (84)

Compound **78** (197 mg, 1.11 mmol) and acetophenone (1.33 g, 11.1 mmol) were dissolved in acetonitrile (180 ml) and placed in a cylindrical *Pyrex* irradiation vessel, equipped with a cooling finger (water cooling). After degassing of the solution with argon for one hour, the reaction mixture was irradiated in a photochemical chamber reactor (type *Rayonet* RPR-208), equipped with 8 lamps (each 24 W, RUL 350 nm, λ_{max}= 350 nm, emission range 300-400 nm). After irradiation for 30 hours, the solvent was evaporated in vacuo and the residue was chromatograped on silica gel with pentane-ether (3:1) to afford the product **84** in a yield of 89% (175 mg) as white crystals.

7,7-Dimethyl-tetrahydro-3a,6a-methano-pentalene-1,4-dione (84):



MS (EI; m/z, rel. int.):
178 (100, M^+, $C_{11}H_{14}O_2$), 136 (88), 135 (97), 121 (55), 93 (86), 91 (27), 80 (25), 79 (38), 77 (25), 39 (22).

HRMS (EI; m/z):
calculated for $C_{11}H_{14}O_2$: 178.099380; found: 178.099544.

^{1}H NMR (400 MHz):
2.65-2.55 (m, 2H, CH_2); 2.36-2.26 (m, 4H, CH_2); 2.04-1.97 (m, 2H, CH_2), 1.29 (s, 6H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):
213.17 (Cq, C-1, 4); 55.58 (Cq, C-8, 9); 43.09 (CH_2, C-2, 5); 34.74 (Cq, C-7); 19.22 (CH_3, C-8, 9); 19.01 (CH_2, C-3, 6).

Mp 13-114 °C.

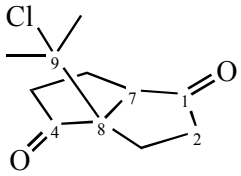
IR (KBr):

3405w, 2932m, 1707s, 1456m, 1406m, 1374w, 1318m, 1289w, 1168m, 1098m, 1042m, 1032m, 1002m.

5.3.9 Treatment of 84 with HCl in HOAc (→ 89a)

162 mg (0.91 mmol) of **84** were dissolved in acetic acid (5 ml) at room temperature and fuming HCl (0.5 ml, 37 %) were added. The mixture was stirred at room temperature for 15 hours, then was washed with sat. sodium hydrogencarbonate solution and dried with anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel using pentane-ether (1:1) as eluating solvent to give white crystalline **89a** (159 mg, 81.4 %) as the first fraction; the second fraction was **78** (page 66) (10 mg, 15 %) as a white crystalline material.

3a-(1-Chloro-1-methyl-ethyl)-hexahydro-pentalene-1,4-dione (89a):



MS (EI; m/z, rel. int.):

214 (14, M^+, $C_{11}H_{15}O_2$), 179 (27), 178 (92), 151 (15), 136 (100), 135 (34), 124 (15), 123 (30), 109(17), 95 (16), 93 (22), 81 (18), 79 (23), 77 (17), 67 (25), 55 (46), 53 (17), 41 (30), 39 (19).

HRMS (EI; m/z):

calculated for $C_{11}H_{15}ClO_2$: 214.076057; found: 214.076257.

^{1}H-NMR (400 MHz):

3.15 (d, J=9.22, 1H, CH); 2.46-2.44 (m, 2H); 2.26-2.09 (m, 6H); 1.69 (s, 3H, CH_3); 1.60 (s, 3H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):

219.24 (Cq, CO); 218.87 (Cq, CO); 73.17 (Cq; C-8); 65.50 (Cq, C-9); 54.33 (CH, C-7); 38.71 (CH_2, C-3); 37.94 (CH_2); 29.54 (CH_3); 28.57 (CH_3); 27.57 (CH_2); 23.32 (CH_2).

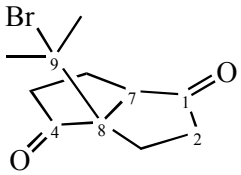
Mp 84.5-85.5 °C.

IR (KBr):
3447w, 2954w, 1733s, 1455w, 1403w, 1391w, 1375w, 1277w, 1225w, 1200w, 1147m, 1105w, 878w, 644w.

5.3.10 Treatment of 84 with HBr in HOAc (→ 89b)

201.5 mg (1.13 mmol) of **84** was dissolved in carbontetrachloride (10 ml) and 0.23 ml HBr (48 %) was added. The mixture was stirred at room temperature for 17 hours and the mixture was washed with sodium hydrogencarbonate and dried with anhydrous sodium sulfate, after evaporation of solvent, the residue was chromatographed on silica gel using pentane-ether (1:1) as eluating solvent to give white crystal **89b** (262 mg, 82.1 %) as the first fraction, the second fraction is **78** (page 66) (82.6 mg, 13 %) as white crystalline material.

3a-(1-Bromo-1-methyl-ethyl)-hexahydro-pentalene-1,4-dione (89b):



MS (EI; m/z, rel. int.):
258 (5, M^+, $C_{11}H_{15}BrO_2$), 179 (100), 151 (27), 123 (22), 55 (46).

HRMS (EI; m/z):
calculated for $C_{11}H_{15}BrO_2$: 258.025555; found: 258.025501.

^{1}H NMR (400 MHz):
3.20 (d, J=9.19, 1H, CH); 2.52-2.47 (m, 2H); 2.32-2.07 (m, 6H); 1.91 (s, 3H, CH_3); 1.82 (s, 3H, CH_3).

^{13}C NMR (^{13}C-COSY):
219.13 (Cq, CO); 218.04 (Cq, CO); 70.87 (Cq, C-8); 66.15 (Cq, C-9); 56.02 (CH, C-7); 39.01 (CH_2); 37.95 (CH_2); 31.37 (CH_3); 30.34(CH_3); 28.73 (CH_2); 23.34 (CH_2).

Mp 108-110 °C.

IR (KBr):

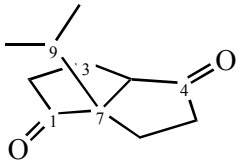
3432m, 2899w, 1729s, 1477w, 1457w, 1412w, 1389w, 1371w, 1285wm 1215w,1179w, 1132w, 1118w, 1102w, 1084w.

5.3.11 Dehalogenation of 89b (→ 90)

(a) 273 mg (1.1 mmol) of **89b** and 0.3 ml triethylamine were dissolved in 20 ml ethylacetate, 101 mg 5% Pt-C was added in a two-necked flask which was connected to water pump and hydrogen-filled balloon. This mixture was evacuated at water pump pressure until evolution of bubbles then the valve of the hydrogen-filled balloon was opened. This process was repeated for several times. Then the reaction was left to react under hydrogen and was monitored by TLC. After the catalyst was filtered, the organic phase was washed with diluted HCl (20%, v/v) and washed with brine, before drying over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel with ether/pentane (1:5). The first fraction contained **90** as colorless liquid (91 mg, 48%) and the second fraction consisted of **78** (73.6 mg, 37%) was the second fraction.

(b) 89b (130 mg, 0.5 mmol) was dissolved in 10 ml dry benzene under argon atmosphere. After adding AIBN (6 mg) and Bu_3SnH (0.27 ml, 1 mmol), the reaction mixture was refluxed for four hours and cooled to room temperature. The reaction mixture was concentrated in vacuo and the residue chromatographed on silica gel with pentane/ether (4:1) to give **90** (68 mg, 75 %).

3a-Isopropyl-hexahydro-pentalene-1,4-dionedione (90):



MS (EI; m/z, rel. int.):

180 (40, M^+, $C_{11}H_{16}O_2$), 152 (16), 137 (100), 125 (72), 110 (18), 109 (45), 82 (23), 81 (25), 79 (14), 67 (19), 55 (21), 41 (24).

HRMS (EI; m/z):

calculated for $C_{11}H_{16}O_2$: 180.115030; found: 180.115244.

^{1}H NMR (400 MHz):

2.65 (m, 1H); 2.33-2.27 (m, 2H); 2.14-2.04 (m, 5H); 1.97-1.85 (m, 2H); 0.90 (d, *J*=6.91, 3H, CH_3); 0.86 (d, *J*=6.81, 3H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):

222.13 (Cq, CO); 220.41 (Cq, CO); 61.06 (Cq, C-7); 52.65 (CH, C-8); 37.91 (CH_2); 37.70 (CH_2); 32.97 (CH, C-9); 27.36 (CH_2); 22.50 (CH_2); 18.18 (CH_3); 17.83 (CH_2).

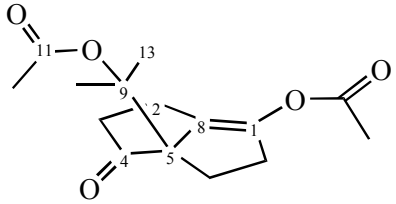
IR (KBr):

3421w, 2964w, 1734s, 1472w, 1408w, 1372w.

5.3.12 Reaction of 84 with borontrifluoride-etherate (→ 96)

$BF_3 \cdot Et_2O$ (*Fluka*, 0.32 ml, 2.5 mmol) was added at –78 °C to a solution of 147 mg (0.827 mmol) of diketone **84** in acetic anhydride (10 ml) under stirring and argon. The mixture was stirred for 6 hours at room temperature, then 15 ml of ice-water were added. The reaction mixture was let to warm slowly to room temperature and was saturated with sodium chloride, then extracted with ether and the organic layer washed with saturated solution of sodium hydrogencarbonate. Before the evaporation of the solvent, the solution was dried over anhydrous sodium sulfate and the residue was chromatographed on silica gel with pentane/ether (1:5) to obtain **96** as a colorless oil (143 mg, 61.6%) and **78** (22 mg, 7%) as crystalline material.

Acetic acid 3a-(1-acetoxy-1-methyl-ethyl)-4-oxo-2,3,3a,4,5,6-hexahydro-pentalen-1yl ester (96):



MS (EI; m/z, rel. int.):

280 (1, M^+, $C_{15}H_{20}O_5$), 222 (11), 180 (37), 179 (14), 178 (22), 150 (13), 139 (12), 138 (100), 137 (11), 43 (56).

HRMS (EI; m/z):

calculated for $C_{15}H_{20}O_5$: 280.131075; found: 280.131273.

^{1}H NMR (400 MHz):

2.95-2.80 (m, 1H); 2.52-2.46 (m, 3H); 2.73-2.05 (m, 2H); 2.12 (s, 3H, CH_3); 1.99-1.91 (m, 2H); 1.89 (s, 3H, CH_3); 1.59 (s, 3H, CH_3); 1.58 (s, 3H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):

217.30 (Cq, C-4); 168.96 (Cq, C-9); 167.63 (Cq, C-10); 146.81 (Cq, C-8); 129.62 (Cq, C-1); 88.07 (Cq, C-5); 67.65 (Cq, C-13); 41.65 (CH_2); 33.85 (CH_2); 28.62 (CH_2); 22.45 (CH_3, C-10); 21.73 (CH_2); 20.60 (CH_3); 20.38 (CH_3); 19.88 (CH_3).

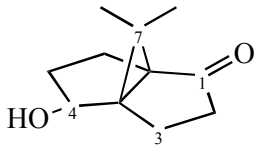
IR (KBr):

3457w, 2944w, 1737s, 1446w, 1386w, 1369m, 1326w, 1251m, 1192s, 1129m, 1052w, 1013w, 935w.

5.3.13 Reduction of 84 with sodium borhydride (→ 97)

84 (350 mg, 1.96 mmol) was dissolved in 15 ml methanol followed by addition of sodium boronhydride (22 mg, 0.59 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 8 hours. After addition of 1 ml of water, the solvent was evaporated and the residue chromatographed on silica gel using pentane/ether (3:1) as eluant to give **97** as white crystals (323 mg, 91.5%).

4-Hydroxy-7,7-dimethyl-tetrahydro-3a,6a-methano-pentalen-1-one (97):



MS (EI; m/z, rel. int.):

180 (34, M^+, $C_{11}H_{16}O_2$), 165 (17), 152 (15), 147 (17), 137 (21), 136 (19), 123 (90), 121 (21), 120 (26), 119 (32), 107 (100), 105 (63), 93 (43), 91 (41), 79 (36), 77 (23), 67 (20), 55 (20), 43 (21), 41 (28), 39 (21).

HRMS (EI; m/z):

calculated for $C_{11}H_{16}O_2$: 180.115030; found: 180.115209.

^{1}H NMR (250 MHz): 4.75 (dd, J=5.62, 9.90, 1H, -CH-); 2.62-2.48 (m, 2H); 2.27-2.16 (m, 2H); 2.10-1.95 (m, 2H); 1.87-1.81 (m, 2H); 1.60-1.50 (m, 1H); 1.41 (s, 3H, CH_3); 1.22 (s, 3H, CH_3).

^{13}C NMR (63 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):
216.47 (Cq, C-1); 82.0 (CH, C-4); 56.96 (Cq, C-8); 53.31 (Cq, C-9); 44.12 (CH_2); 42.28 (CH_2); 35.25 (Cq, C-7); 25.41 (CH_2); 24.10 (CH_2); 20.72 (CH_3); 20.63 (CH_3).

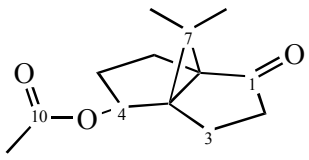
Mp 97-98 °C.

IR (KBr):
3354s (br.), 2944m, 1713s, 1448w, 1404w, 1327w, 1281w, 1099w, 1059m, 1042m, 1025m, 1009w, 669w.

5.3.14 Esterification of 97 (→ 98)

Hydroxyketone **97** (169 mg, 0.95 mmol) was dissolved in 5 ml pyridine at room temperature and heated at 88-90 °C for 2 hours. After distilling off the solvent, the residue was dissolved in 10 ml ethyl acetate and washed with brine. Next, drying over sodium sulfate and evaporation of the solvent in vacuo followed. Chromatography of the residue on silica gel gave **98** as white crystals (174 mg, 83%).

Acetic acid 7,7-dimethyl-4-oxo-tetrahydro-3a,6a-methano-pentalen-1-yl ester (98):



MS (EI; m/z, rel. int.):
222 (5, M^+, $C_{13}H_{18}O_3$), 180 (34), 179 (17), 162 (46), 136 (15), 134 (45), 121 (16), 120 (69), 119 (100), 107 (34), 106 (17), 105 (86), 93 (20), 91 (38), 79 (20), 77 (17), 43 (63), 41 (20).

HRMS (EI; m/z):

calculated for $C_{13}H_{18}O_3$: 222.125595; found: 222.125440.

^{1}H NMR (400 MHz):

5.36 (dd, *J*=5.03, 10.21, 1H); 2.75-2.60 (m, 1H); 2.59-2.53 (m, 1H); 2.28-2.20 (m, 2H); 2.15-2.07 (m, 2H); 2.0 (s, 3H, CH_3); 1.91-1.84 (m, 1H); 1.79-1.61 (m, 1H); 1.33 (s, 3H, CH_3); 1.23 (s, 3H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):

215.24 (Cq, C-1); 171.06 Cq, C-10); 83.22 (CH, C-4); 56.59 (Cq, C-8); 53.94 (Cq, C-9); 43.22 (CH_2); 38.79 (CH_2); 34.77 (Cq, C-9); 25.14 (CH_2); 23.31 (CH_2); 20.99 (CH_3, C-11); 20.03 (CH_3); 19.73 (CH_3).

Mp 82-83 °C.

IR (KBr):

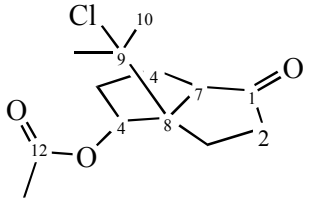
3450m (br), 2950m, 2918m, 1736s, 1707s, 1457w, 1407w, 1377m, 1351w, 1325m, 1280m, 1251s, 1098m, 1050m, 1023s.

5.3.15 Treatment of 98 with HCl in HOAc (→ 102-105)

At room temperature, **98** (410 mg, 1.85 mmol) was dissolved in 10 ml CCl_4 under stirring, then 0.2 ml fuming hydrochloric acid (37%) was added. This mixture was stirred for further 12 hoursat room temperature before washing it with saturated sodium hydrogencarbonate solution. The concentrated residue was chromatographed on silica gel with pentane/ether (5:1) to give the following 4 products:

Product **102**: 127 mg (26.6%), pale yellow oil.

Acetic acid 6a-(1-chloro-1-methyl-ethyl)-4-oxo-octahydro-pentalen-1-yl ester (102):



MS (EI; m/z, rel. int.):

258 (7, M^+, $C_{13}H_{19}ClO_3$), 222 (13), 198 (15), 181 (19), 180 (100), 163 (21), 152 (56), 137 (29), 136 (55), 123 (18), 121 (20), 107 (17), 93 (18), 79 (19), 43 (67), 41 (16).

HRMS (EI; m/z):

calculated for $C_{13}H_{19}ClO_3$: 258.102273; found: 258.102449.

^{1}H NMR (500 MHz):

5.12-5.10 (m, 1H, CH_3); 2.91-2.88 (m, 1H, CH); 2.56-2.50 (m, 3H); 2.35-2.33 (m, 2H); 2.25-2.05 (m, 1H); 2.04 (s, 3H, CH_3); 1.90-1.80 (m, 2H); 1.79 (s, 3H, CH_3); 1.69 (s, 3H, CH_3).

^{13}C NMR (^{1}H; ^{13}C-COSY):

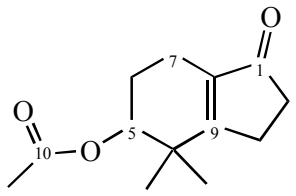
221.13 (Cq, C-1); 169.68 (Cq, C-12); 82.95 (CH, C-4); 62.98 (Cq, C-9); 54.33 (Cq, C-8); 41.09 (CH, C-7); 37.80 (CH_2); 32.21 (CH_2); 30.96 (CH_2); 29.38(CH_3); 28.46 (CH_3); 27.82 (CH_2); 21.46 (CH_3).

IR (KBr):

3448w, 2978w, 1737s, 1637w, 1458w, 1391w, 1374w, 1239s, 1144w, 1039w.

Product **103**: 59 mg (14.4%), pale yellow oil.

Acetic acid 4,4-dimethyl-1-oxo-2,3,4,5,6,7-hexahydro-1H-inden-5-yl ester (103):



MS (EI; m/z, rel. int.):

222 (48, M^+, $C_{13}H_{18}O_3$), 180 (84), 162 (100), 152 (85), 147 (63), 137 (46), 136 (89), 135 (22), 121 (23), 120 (42), 119 (50), 105 (61), 93 (26), 91 (25), 79 (19), 77 (19), 43 (78), 41 (17).

HRMS (EI; m/z):

calculated for $C_{13}H_{18}O_3$: 222.125646; found: 222.125595.

^{1}H NMR (400 MHz):

4.89-4.91 (m, 1H, CH); 2.50-2.51 (m, 2H, CH_2); 2.40-2.37 (m, 2H, CH_2); 2.20-2.17 (m, 2H, CH_2); 2.04 (s, 3H, CH_3); 1.86-1.84 (m, 2H, CH_3); 1.15 (s, 3H, CH_3); 1.13 (s, 3H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):

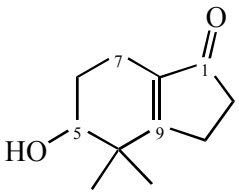
208.67 (Cq, C-1); 176.67 (Cq, C-10); 170.57 (Cq, C-9); 136.52 (Cq, C-8); 76.55 (CH, C-5); 38.40 (Cq, C-4); 34.54 (CH_2); 25.45 (CH_3, C-11); 24.87 (CH_2); 22.97 (CH_2); 21.60 (CH_3); 21.07 (CH_3); 17.30 (CH_2).

IR (KBr):

3457w, 2968w, 1736s, 1700s, 1641m, 1374w, 1244s, 1046w, 1033w.

Product **104**: 47.5 mg (14.3%), pale yellow oil.

5-Hydroxy-4,4-dimethyl-2,3,4,5,6,7-hexahydro-inden-1-one (104):



MS (EI; m/z, rel. int.):

180 (100, M^+, $C_{11}H_{16}O_2$), 152 (48), 137 (48), 136 (88), 135 (37), 123 (10), 121 (40), 93 (44), 91 (18), 79 (21), 77 (17), 55 (10), 43 (15), 41 (14), 39 (11).

HRMS (EI; m/z):

calculated for $C_{11}H_{16}O_2$: 180.115030; found: 180.115261.

^{1}H NMR (400 MHz):

3.67 (m, 1H); 2.51-2.48 (m, 2H); 2.38-2.36 (m, 2H); 2.24-2.05 (m, 2H); 1.95-1.85 (m, 2H); 1.64 (s, 1H, HOC-3); 1.17 (s, 3H, CH_3); 1.14 (s, 3H, CH_3).

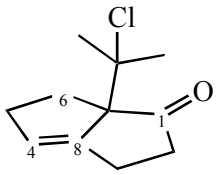
^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):

209.00 (Cq, C-1); 178.02 (Cq, C-9); 136.26 (Cq, C-8); 75.16 (CH, C-5); 39.58 (Cq, C-4); 34.70 (CH_2); 26.20 (CH_2); 25.17 (CH_3); 25.04 (CH_2); 20.74 (CH_3); 17.67 (CH_2).

IR (KBr):
3431s, 2965m, 2934m, 2870m, 1673s, 1628s, 1437w, 1389w, 1231w, 1175s, 1051m.

Product **105:** 37.5 mg (10.2%), pale yellow oil.

6a-(1-Chloro-1-methyl-ethyl)-3,5,6,6a-tetrahydro-2Hpentalen-1-one (105):



MS (EI; m/z, rel. int.):
198 (54, M^+, $C_{11}H_{15}ClO$), 163 (14), 156 (21), 121 (100), 119 (61), 107 (29), 91 (34).

HRMS (EI; m/z):
calculated for $C_{11}H_{15}ClO$: 198.081143; found: 198.081080.

^{1}H NMR (500 MHz):
5.85 (dd, J=1.58, 1.36); 2.91-2.67 (m, 1H); 2.56-2.52 (m, 2H); 2.44-2.34 (m, 2H); 2.10-2.06 (m; 1H); 1.94-1.89 (m, 1H); 1.71 (s, 3H, CH_3); 1.60 (s, 3H, CH_3).

^{13}C NMR (125.8 MHz, BB, DEPT):
217.24 (Cq, C-1); 148.53 (Cq, C-8); 129.50 (CH, C-4); 73.01 (Cq, C-9); 70.95 (Cq, C-7); 42.47 (CH_2); 34.75 CH_2); 33.42 (CH_2); 29.43 (CH_3); 28.62 (CH_3); 24.99 (CH_2).

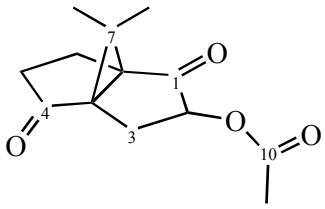
IR (KBr):

3445w, 2987w, 2939m, 1735s, 1658w, 1459w, 1443w, 1393w, 1387w, 1371m, 1208m, 1102w, 805m.

5.3.16 Oxidation of diketone 84 with lead tetraacetate (→ 115 and 116)

Diketone **84** (179 mg, 1 mmol) was dissolved in 20 ml benzene, then 700 mg (1.5 mmol) lead tetraacetate (95%, *Acros*) and 5 ml acetic acid were added and the mixture was stirred at room temperature for 6 days. After adding 15 ml of water, the organic phase was separated and the aqueous phase was extracted with ether. The combined organic layers were washed with saturated sodium hydrogencarbonate solution and brine. Before evaporating the solvent, the organic phase was dried over anhydrous sodium sulfate and the organic layer concentrated. The residue was chromatographed on silica gel with pentane/ether (1:3) to give **115** (123 mg, 53%) and **116** (47 mg, 16%) as whit crystalline materials.

Acetic acid 7,7-dimethyl-1,4-dioxo-tetrahydro-3a,6a-methano-pentalen-2-yl ester (115):



MS (EI; m/z, rel. int.):

236 (0.3, M^+, $C_{13}H_{16}O_4$), 194 (35), 179 (50), 176 (100), 166 (58), 137 (25), 134 (69), 133 (22), 123 (60), 105 (31), 91 (33), 79 (26), 77 (22), 55 (18), 43 (78), 41 (19).

HRMS (EI; m/z):

calculated for $C_{13}H_{16}O_4$: 236.104860; found: 236.104930.

^{1}H NMR (400 MHz):

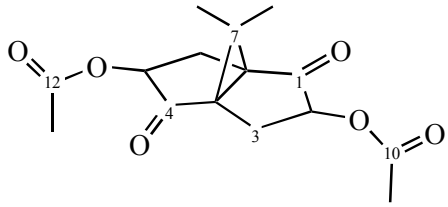
4.51 (dd, J=4.99, 8.46, 1H); 2.75-2.69 (m, 1H); 2.58-2.17 (m, 5H); 2.03 (s, 3H, CH_3); 1.29 (s, 3H, CH_3); 1.23 (s, 3H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):
212.86 (Cq, C-1); 207.70 (Cq, C-4); 170.26 (Cq, C-10); 81.37 (CH, C-2); 54.16 (Cq, C-8); 53.55 (Cq, C-9); 42.30 (CH_2); 35.65 (Cq, C-7); 27.99 (CH_2); 20.60 (CH_3); 20.33 (CH_3); 19.70 (CH_2); 19.44 (CH_3).

Mp 110-111 °C.

IR (KBr):
3442w (br.), 2957w, 1726s, 1383w, 1314w, 1229m, 1195w, 1071w, 1027w.

Acetic acid 5-acetoxy-7,7-dimethyl-1,4-dioxo-tetrahydro-3a,6a-methano-pentalen-2-yl ester (116):



MS (EI; m/z, rel. int.):
294 (4, M^+, $C_{15}H_{18}O_6$), 252 (13), 224 (27), 195 (15), 177 (19), 174 (38), 164 (33), 149 (32), 136 (31), 135 (19), 121 (22), 93 (10), 91 (10), 43 (100).

HRMS (EI; m/z):
calculated for $C_{15}H_{18}O_6$: 294.110340; found: 294.110090.

^{1}H NMR (400 MHz): 4.84 (dd, J=4.55, 8.50, 2H); 2.58 (dd, J=8.45, 14.80, 2H); 2.30 (dd, J=4.54, 14.83, 2H); 2.07 (s, 6H, CH_3); 1.32 (s, 6H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):
206.14 (Cq, C-1,4); 170.09 (Cq, C-12, 14); 79.17 (CH, C-2,5); 51.74 (Cq, C-8, 9); 36.29 (Cq, C-7); 28.04 (CH_2, C-4, 6); 20.88 (CH_3); 20.43 (CH_3).

Mp 162-163 °C.

IR (KBr):
3456w (br.), 2953w, 1730s, 1448w, 1377w, 1231s, 1167w, 1067w, 1022m.

5.3.17 Birch Reduction of 84 (→ 123)

Liquid ammonia (50 ml) was distilled into a three-necked flask, cooled to –78 °C, followed by addition of 57 mg (8.21 mmol) lithium which resulted in the formation of a deep blue solution. To this solution was added a solution of diketone **84** (92 mg, 0.52 mmol) in 5 ml dry THF, then the reaction was stirred for further 2 hours. After adding 1 g of sodium chloride, the solution was slowly warmed to room temperature. Ammonia was evaporated and 15 ml water were added. The mixture was extracted with ethyl acetate and the organic layers dried over anhydrous sodium sulfate. After evaporation of the solvent at reduced pressure, the residue was chromatographed on silica gel with pentane/ether (1:3) to give **123** (58 mg, 60.2%) as white a crystalline product.

5.3.18 Reduction of 84 with sodium in toluene-isopropanol (→ 123)

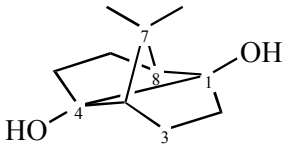
Sodium was heated in 7.5 ml toluene to reflux under vigorous stirring and argon to give finely dispersed sodium, then a solution of diketone **84** (92 mg, 0.516 mmol) in 253 ml isopropanol was added, the solution kept under reflux and 3.5 hours later additional 99 mg of sodium and 311 mg isopropanol were added and the stirring was continued for further 2 hours. After cooling the reaction mixture to room temperature, 4 ml ethanol was added to destroy the excess sodium. Next, 20 ml saturated NH_4Cl solution was added, the organic phase was separated after extraction and the water phase was separately extracted with ether. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Chromatography of the residue on silica gel with pentane/ether (1:3) afforded **123** (64 mg, 68%) as a white crystalline product.

5.3.19 Reduction of 84 with sodium in ether saturated by $NaHCO_3$ (→ 123)

To a solution of diketone **84** (89 mg, 0.5 mmol) in 10 ml diethylether was added 1 ml of saturated sodium bicarbonate solution and sodium was carefully added in a small pieces at 0 ºC under stirring. After the initial sodium disappeared sodium, further small pieces of sodium were added until the reaction was completed (monitored by TLC). Thereafter water was added ml by ml until no further reaction with sodium was observed; a total of 4.6 mg (198.98 mmol) sodium was consumed. Then, the organic phase was separated and the aqueous phase

was extracted repeatedly with ether and dried over sodium sulfate. After concentration, the residue was purified by chromatography on silica gel using pentane/ether (1:3) as eluent to give **123** (76.1 mg, 83.5%) as a white crystalline product.

7,7-Dimethyl-tetrahydro-1,4-methano-pentalene-3a,6a-diol (123):



MS (EI; m/z, rel. int.):
182 (98, M^+, $C_{11}H_{18}O_2$), 167 (44), 164 (47), 149 (44), 122 (23), 121 (28), 111 (83), 109 (37), 107 (47), 106 (21), 99 (22), 98 (20), 96 (96), 93 (28), 84 (21), 83 (74), 79 (28), 70 (20), 69 (100), 67 (24), 55 (55), 43 (54), 41 (64).

HRMS (EI; m/z):
calculated for $C_{11}H_{18}O_2$: 182.130680; found: 182.130416.

^{1}H NMR (250 MHz):
1.91-1.87 (m, 2H); 1.58-1.51 (m, 6H); 1.36-1.31 (m, 2H); 0.92 (s, 6H, CH_3).

^{13}C NMR (63 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):
84.90 (Cq, C-1, 4); 49.71 (CH, C-8,9); 31.62 (Cq, C-7); 26.70 (CH_2); 24.99 (CH_3); 21.76 (CH_2).

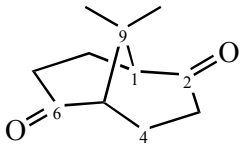
Mp 149-150 °C.

IR (KBr):
3417s (br.), 2955m, 1636w, 1384m, 1128m, 1062w.

5.3.20 Oxidation of pinacol 123 with lead tetraacetate (→ 85)

To a suspension of **123** (36 mg, 0.2 mmol) in 10 ml absolute benzene was added lead tetraacetate (95%, *Fluka*, 131 mg, 0.28 mmol) with stirring at room temperature and under argon. After stirring for 6.5 hours, 0.3 ml glycerine was added and the mixture was warmed to 45 °C to destroy the excess of lead tetraacetate. The mixture was filtered by washing the residue with toluene. The combined organic layers were dried over anhydrous sodium sulphate prior to evaporation of the solvents. Chromatography of the residual crude product on silica gel with pentane/ether (1:4) gave the desired **85** with 57% yield (20.6 mg).

9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione (85):



MS (EI; m/z, rel. int.):
180 (27, M^+, $C_{11}H_{16}O_2$), 137 (11), 112 (92), 95 (10), 82 (14), 81 (15), 69 (100), 67 (19), 55 (19), 41 (30).

HRMS (EI; m/z):
calculated for $C_{11}H_{16}O_2$: 180.115030; found: 180.115276.

^{1}H NMR (400 MHz):
2.56 (dd, 1H, J=7.9Hz, J=18.1Hz); 2.38-2.28 (m, 2H); 2.18-2.12 (m, 1H); 1.88 (dd, 1H, J=9.5Hz, J=14.5Hz); 0.97 (s, 6H, CH_3).

^{13}C NMR (100.6 MHz, BB, DEPT, ^{1}H; ^{13}C-COSY):
212.89 (Cq, C-2,6); 54.72 (C-1,5); 37.25 (Cq, C-9); 36.04 (CH_2, C-3,7); 26.25 (CH_3, C-10,11); 22.57 (CH_2, C-4,8).

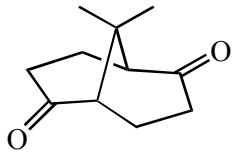
Mp 140-141 °C.

IR (KBr):
3440w (br), 2965w, 2910m, 1692s, 1458w, 1435w, 1326w, 1235w, 1031w, 744w.

5.3.21 Synthesis of 9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione (85) from 84

Graphite (970 mg, 70.76 mmol) was placed in a two-necked flask and heated under argon atmosphere to degas for 20 min at 160 °C before freshly cut potassium (390 mg, 9.98 mmol) was added under vigorous stirring. Bronze-colored laminate of graphite and potassium (C_8K) was formed. After cooling to room temperature, 20 ml dry THF was added by syringe. To this suspension was added solution of **84** (358 mg, 2.0 mmol) in 20 ml of dry THF at room temperature and stirred for 5 days at the same temperature. After adding 5 ml MeOH, graphite was filtered off and washed extensively with ethyl acetate, the organic phase was concentrated in vacuo and chromatographed on the silica gel with pentane-ether (5:1) to give white crystalline **85** (1.18 mmol, 212 mg, 59%).

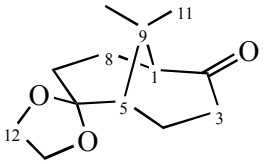
9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione (85),
(data see p. 83):



5.3.22 Synthesis of 131

A mixture of 9,9-dimethyl-bicyclo[3.3.1]nonane-2,6-dione (**85**) (0.678 g, 3.76 mmol), 1,2-ethanediol (**130**) (0.233 g, 3.76 mmol) and *p*-TsOH monohydrate (0.071 g, 0.37 mmol) in 200 ml of toluene was vigorously stirred and refluxed for 4.5 hours in a *Dean-Stark* apparatus. After cooling, reaction mixture was washed with saturated aq. $NaHCO_3$ (60 ml) and NaCl (2 x 50 ml). After drying over anhydrous Na_2SO_4, the solvent was evaporated in vacuo and the residue chromatographed on silica gel with pentane/ether (1:2) as eluent to give the product **131** (53 mg, 63 % yield) as a crystalline material.

Monoketal 131:



131

MS (EI; m/z, rel. int.):
224 (10.2, M^+, $C_{13}H_{20}O_3$), 100 (99), 86 (54.5), 55 (16.2).

HRMS (EI; m/z):
calculated for $C_{13}H_{20}O_3$: 224.141245; found: 224.141486.

^{1}H NMR (400 MHz, ^{1}H-^{1}H-COSY, $CDCl_3$):
3.97-3.78 (m, 4H); 2.39 (dd, 1H, J=9.2Hz, J=19.2Hz); 2.25 (dd, 1H, J=9.7Hz, J=19.2Hz); 2.17-2.11 (m, 1H); 2.04-1.85(m, 3H); 1.16 (s, CH_3), 0.91 (s, CH_3).

^{13}C NMR (100 MHz, BB, DEPT, ^{1}H-^{13}C-COSY, $CDCl_3$):
215.95 (Cq, C-1); 110.87 (Cq, C-6); 64.64 (CH_2, C-12); 63.30 (CH_2, C-13); 55.70 (CH, C-1); 44.72 (CH, C-5); 36.43 (CH_2); 35.66 (Cq, C-9); 30.66 (CH_2); 29.22 (CH_3); 26.74 (CH_3); 22.44 (CH_2); 20.59 (CH_2).

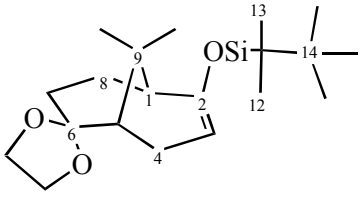
IR (KBr):
3454 (br.), 3011m, 2960s, 2974s, 1693s, 1455m, 1102s, 909m.

Mp 53 °C.

5.3.23 Synthesis of 132

To a solution of the monoprotected diketone **131** (61 mg, 0.272 mmol) in CH_2Cl_2 (8 ml), TBDMSOTf (0.057 ml, 86.2 mg, 0.323 mmol), followed by NEt_3 (0.094 ml, 0.69 mg, 0.68 mmol), were added dropwise at room temperature. After stirring for 10 min at room temperature, the mixture was hydrolyzed with water (5 ml) and extracted with CH_2Cl_2 (3x 20 ml). The combined organic layers were dried with $NaSO_4$. After filtration, the solvents were removed under reduced pressure at 25 °C. The crude product was purified by chromatography on a silica gel column with pentane as eluent to give the silylated enol ether **132** (0.09 g, 0.272 mmol, quantitative yield).

Siliylenol ether 132:



132

MS (EI; m/z, rel. int.):
338 (54.0, M^+, $C_{19}H_{34}O_3Si_1$), 294 (20.1), 293 (85.9), 99 (100.0), 75 (21.8), 73 (47.0), 55 (17.0).

HRMS ESIpos : m/z calcd for $C_{19}H_{34}NaO_3Si_1$ (M+Na):
calculated: 361.217066, found: 361.217493.

^{1}H NMR (400 MHz, ^{1}H-^{1}H-COSY, $CDCl_3$):
4.69 (dd, 1H, J=2.7, 4.6Hz); 3.99-3.81 (m, 4H, CH_2); 2.24 (dd, 1H, J=4.6Hz, J=17.9Hz); 2.11 (ddd, 1H, J=2.7Hz, J=6.3Hz, J=18.0Hz); 1.87 (t, 1H, J=13.1Hz); 1.75 (dt, 1H, J=5.4Hz, J=13.3Hz); 1.62 (s, 1H); 1.56-1.45 (m, 2H); 1.35 (d, 1H, J=5.4Hz); 1.14 (s, CH_3); 0.99 (s, CH_3); 0.89 (s, 9H); 0.12 (s, CH_3); 0.10 (s; CH_3).

^{13}C NMR (100 MHz, BB, DEPT, ^{1}H-^{13}C-COSY, $CDCl_3$):
150.56 (Cq, C-2); 112.36 (Cq, C-6); 100.92 (CH, C-3); 64.45 (CH_2); 63.00 (CH_2); 45.56 (CH); 44.44 (CH); 34.52 (Cq); 28.16 (CH_3); 28.13 (CH_2); 26.91 (CH_3); 25.73 (CH_3, C-15,16,17), 24.43 (CH_2); 22.21 (CH_2); 17.95 (Cq, C-14); -4.10 (CH_3), -4.49 (CH_3).

IR 3399 (br.) 2910s, 1706s, 1459m, 1435m, 1325m.

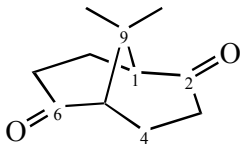
Mp 44 °C.

5.3.24 Attempted $ZrCl_4$-catalyzed [2+2] reaction of 132 and methyl but-2-ynoate (133)

$ZrCl_4$ (0.11 mg, 0.49 mmol) was suspended in CH_2Cl_2 (10 ml) and Et_2O (1 ml) and then methyl but-2-ynoate (**133**) (0.051 ml, 50.5 mg, 0.51 mmol) was added. The resulting mixture was cooled to -78 °C, whereupon a solution of enol ether **132** (83 mg, 0.24 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring for 10 min at -78 °C and for 10 min at room temperature, the mixture was hydrolyzed by the addition of saturated aqueous $NaHCO_3$ solution (5 ml). After extraction with Et_2O (3 x 30 ml), the combined organic layers were dried with $NaSO_4$ and the solvents were removed at reduced pressure. The crude product was

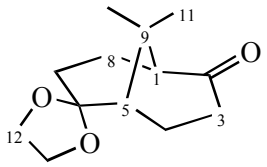
chromatographed on silica gel with pentane:ether (10:1). Instead of the expected [2+2] product, **85** and **131** were recovered with 45 and 41% yield, respectively.

9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione (85), (data see p. 83):



85

Monoketal 131, (data see p. 84):

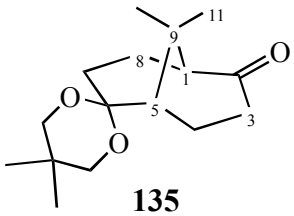


131

5.3.25 Synthesis of 135

Diketone **85** (0.203 g, 1.13 mmol), 2,2-dimethylpropane-1,3-diol (**134**) (0.12 g, 1.13 mmol), and *p*-TsOH (0.023 g, 0.01 mmol) were dissolved in toluene (50 ml). The resulting mixture was refluxed for 17 hours with a *Dean-Stark* head. It was then cooled to 0 °C, diluted with Et_2O (10 mL), and then 10% aq. NaOH solution (3 mL) was added. After extraction with Et_2O (2 x 50 mL), the organic layers were collected, washed with saturated aqueous NaCl solution (100 ml), and dried with Na_2SO_4. Volatile components were then removed at reduced pressure. The crude material was purified by chromatography on a silica gel column with pentane: ether (10:1) as eluent and 0.27 g **135** was obtained (62% yield).

Monoketal 135:



135

MS (EI; m/z, rel. int.):
226 (10.7, M^+, $C_{16}H_{26}O_3$), 142 (12.6), 141 (100), 128 (36.5), 69 (35.3), 55 (21.9), 41 (23.7).

HRMS (EI; m/z):
calculated for $C_{16}H_{26}O_3$: 266.188195; found: 226.187915.

^{1}H NMR (400 MHz, ^{1}H-^{1}H-COSY, $CDCl_3$): 3.57 (d, 2H, J=11.4Hz); 3.50 (d, 2H, J=11.3Hz); 2.52 (dd, 1H, J=7.9Hz, J=17.8Hz); 2.36 (dd, 1H, J=9.0Hz, J=20.4Hz); 2.24-1.95 (m, 5H); 1.50-1.37 (m, 1H); 1.14 (s, 6H, CH_3); 1.1 (s, CH_3), 0.78 (s, CH_3).

^{13}C NMR (100 MHz, BB, DEPT, ^{1}H-^{13}C-COSY, $CDCl_3$): 212.85 (Cq, C-2); 99.86 (Cq, C-6); 69.76 (CH_2, C-12); 69.56 (CH_2, C-13); 56.22 (CH, C-1); 54.64 (CH, C-5); 36.51 (CH_2); 31.90 (CH_2); 36, 40 (Cq); 30.25 (Cq); 29.83 (CH_3); 26.04 (CH_2); 23.09 (CH_3); 22.34 (CH_2).

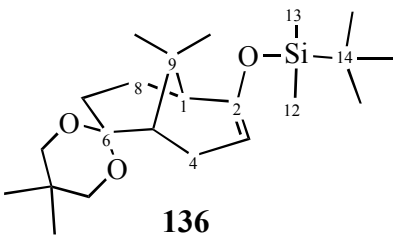
IR (KBr):
3416 (br.), 2912s, 2854m, 1704m, 1459m, 1261m, 1031m.

Mp 47 °C.

5.3.26 Synthesis of 136

To a solution of the monoketal **135** (0.224 g, 0.84 mmol) in CH_2Cl_2 (40 ml), TBDMSOTf (0.194 ml, 0.223 g, 0.84 mmol) followed by NEt_3 (0.292 ml, 0.21 g, 2.11 mmol) were added dropwise at room temperature. After stirring for 10 min at room temperature, the mixture was hydrolyzed with water (10 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic layers were dried with Na_2SO_4. After filtration, the solvents were removed at reduced pressure and the crude product was purified by chromatography on a silica gel column with pentane:ether (10:1) as eluent to give the silylated enol ether **136** (0.2355 g, quantitative yield).

Silylenol ether 136:



136

MS (EI; m/z, rel. int.):
380 (57.2, M^+, $C_{22}H_{40}O_3Si$), 295 (10.7), 294 (32.3), 293 (100), 141 (87.7), 75 (15.9), 73 (34.2), 69 (17.8), 55 (20.9).

^{1}H NMR (250 MHz, ^{1}H-^{1}H-COSY, $CDCl_3$): 4.68 (t, 1H, J=3.5Hz); 3.60 (d, 2H, J=11.4Hz); 3.49 (d, 2H, J=11.1Hz); 2.14-2.07 (m, 3H); 1.96-1.42 (m, 5H); 1.23 (s, 6H, CH_3); 1.13 (s, CH_3), 1.06 (s, CH_3); 0.9 (s, 9H, CH_3); 0.11 (s, CH_3), 0.99 (s, CH_3).

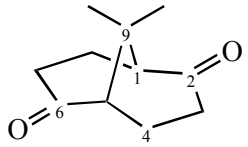
^{13}C NMR (63 MHz, BB, DEPT, ^{1}H-^{13}C-COSY, $CDCl_3$): 150.52 (Cq, C-2); 101.12 (Cq, C-6); 100.80 (CH, C-3); 69.57 (CH_2); 69.34 (CH_2); 45.99 (CH); 35.80 (CH); 34.18 (Cq); 30.03 (CH_2); 29.66 (CH_2); 29.62 (Cq); 28.95 (CH_3); 26.08 (CH_3); 25.69 (3C; CH_3); 23.31 (CH_3); 23.16 (CH_2); 22.38 (CH_3); -4.087 (CH_3); -4.57 (CH_3).

IR (KBr):
2927s, 2856m, 1666m, 1483m, 1361m, 1206m, 1146m, 1104s, 837m.

5.3.27 Attempted $ZrCl_4$-catalyzed [2+2] reaction of 136 and methyl but-2-ynoate (133)

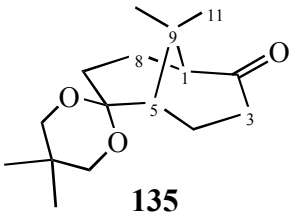
$ZrCl_4$·THF (143 mg, 0.378 mmol) was suspended in CH_2Cl_2 (10 ml) and Et_2O (1 ml) and then methyl but-2-ynoate (**133**) (0.044 ml, 43 mg, 0.43 mmol) was added. The resulting mixture was cooled to -78 °C, whereupon a solution of enol ether **136** (100 mg, 0.27 mmol) in CH_2Cl_2 (1 ml) was added dropwise. After stirring for 10 min at -78 °C and for 10 min at room temperature, the mixture was hydrolyzed by the addition of saturated aqueous $NaHCO_3$ solution (5 ml). After extraction with Et_2O (3 x 30 ml), the combined organic layers were dried with $NaSO_4$ and the solvents were removed at reduced pressure. The crude product was chromatographed on silica gel with pentane:ether (10:1) as eluent. Instead of the expected [2+2] product, **85** and **135** were recovered with 43 and 42 % yield, respectively.

9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione (85),
(data see p. 83):



85

Monoketal 135 (data see p. 87):

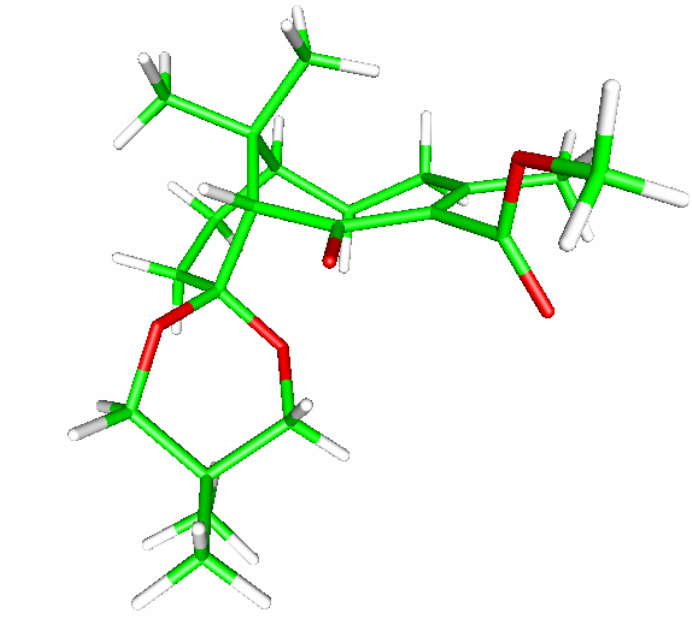


135

5.4 Quantum mechanical calculations

Cartesian coordinates of the optimized molecules are represented. Geometry optimizations were performed for both structures, **138** and **145**, employing density functional theory and the TURBOMOLE program package. The structures were plotted employing GOPENMOL. BP is a fast density functional that has proven to give accurate geometrical parameters in many application studies. For the geometry optimization of **138** and **145**, the SV(P) basis sets were used. Complete geometry optimization, i.e. no geometrical parameters were fixed. One reasonable conformer was studied. All calculations were performed in vacuum. This is expected to be a good approximation since aprotic solvent THF will be used in the experiment. Furthermore, only charge neutral systems were investigated.

5.4.1 Data for the compound 138



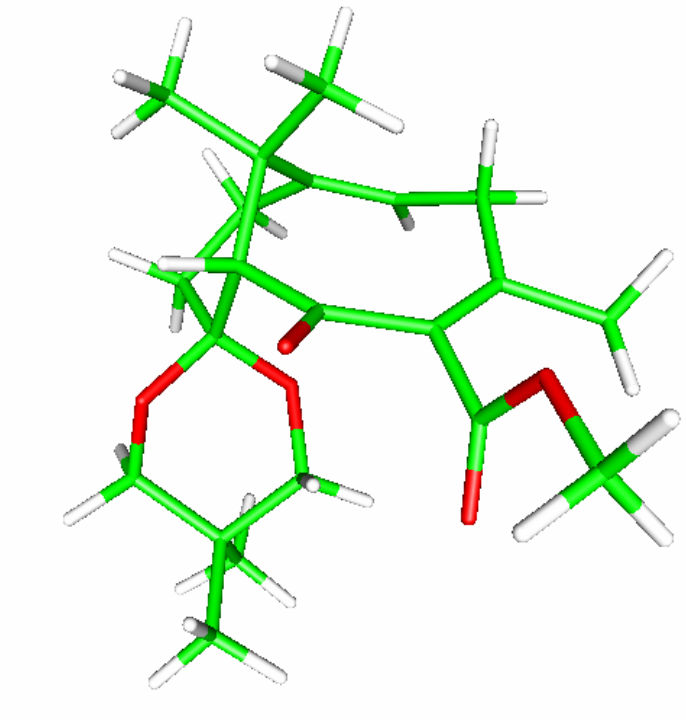
Cartesian coordinates of structure 138 (Ångstroms)

Atom	x	y	z
C	-0.5355	1.0939	-0.9823
C	-0.8031	-0.6934	-2.5893
C	-2.3037	-0.8878	-2.4758
H	-2.8337	-0.5846	-3.4075
C	-0.3833	0.7766	-2.5239
C	0.0022	-1.7534	-2.3600
H	-0.7934	2.1675	-0.8710
H	-2.5205	-1.9643	-2.3196
C	-2.8467	-0.0507	-1.2793
H	-3.6222	-0.6299	-0.7375
C	-1.7409	0.3329	-0.2683
H	-0.4990	-2.7317	-2.2377
C	1.4876	-1.7862	-2.1031
H	2.0448	-1.1971	-2.8670
H	1.8345	-2.8309	-2.2491
C	2.0020	-1.3350	-0.7311
C	1.7028	-0.1981	-0.0220
C	0.7905	0.9997	-0.2037
O	1.1579	2.0203	0.3888
C	-1.3122	1.6909	-3.3735
H	-2.3859	1.6341	-3.1124
H	-1.0046	2.7524	-3.2507

H	-1.2124	1.4342	-4.4518
C	1.0373	1.1320	-3.0334
H	1.8671	0.7100	-2.4366
H	1.1607	0.8046	-4.0891
H	1.1703	2.2355	-3.0041
C	3.0744	-2.2800	-0.2224
H	3.5066	-1.9993	0.7573
H	2.6471	-3.3049	-0.1260
H	3.9071	-2.3551	-0.9606
C	2.5516	0.0956	1.2128
O	2.2122	-0.0998	2.3661
O	3.7614	0.5973	0.8639
C	4.5994	0.9959	1.9596
H	4.1026	1.7900	2.5568
H	4.8210	0.1343	2.6263
H	5.5308	1.3817	1.5009
O	-2.2181	1.2713	0.6916
O	-1.3692	-0.8861	0.3740
C	-3.0515	0.6957	1.7001
H	-3.9388	0.2014	1.2372
H	-3.4223	1.5574	2.2940
C	-2.2666	-0.3147	2.5939
C	-1.0314	-0.7366	1.7583
H	-0.6491	-1.7279	2.0780

H	-0.2047	-0.0072	1.8980
C	-1.7855	0.3573	3.8940
H	-2.6452	0.6192	4.5520
H	-1.1110	-0.3158	4.4698
H	-1.2200	1.2898	3.6730
C	-3.1570	-1.5320	2.9050
H	-3.4024	-2.0899	1.9735
H	-2.6451	-2.2347	3.6007
H	-4.1149	-1.2236	3.3832
H	-3.3238	0.8914	-1.6179

5.4.2 Data for the compound 145



Cartesian coordinates of structure 145 (Ångstroms)

Atom	x	y	z
C	-0.5355	1.0939	-0.9823
C	-0.8031	-0.6934	-2.5893
C	-2.3037	-0.8878	-2.4758
H	-2.8337	-0.5846	-3.4075
C	-0.3833	0.7766	-2.5239
C	0.0022	-1.7534	-2.3600
H	-0.7934	2.1675	-0.8710
H	-2.5205	-1.9643	-2.3196
C	-2.8467	-0.0507	-1.2793
H	-3.6222	-0.6299	-0.7375
C	-1.7409	0.3329	-0.2683
H	-0.4990	-2.7317	-2.2377
C	1.4876	-1.7862	-2.1031
H	2.0448	-1.1971	-2.8670
H	1.8345	-2.8309	-2.2491
C	2.0020	-1.3350	-0.7311
C	1.7028	-0.1981	-0.0220
C	0.7905	0.9997	-0.2037
O	1.1579	2.0203	0.3888
C	-1.3122	1.6909	-3.3735
H	-2.3859	1.6341	-3.1124
H	-1.0046	2.7524	-3.2507

H	-1.2124	1.4342	-4.4518
C	1.0373	1.1320	-3.0334
H	1.8671	0.7100	-2.4366
H	1.1607	0.8046	-4.0891
H	1.1703	2.2355	-3.0041
C	3.0744	-2.2800	-0.2224
H	3.5066	-1.9993	0.7573
H	2.6471	-3.3049	-0.1260
H	3.9071	-2.3551	-0.9606
C	2.5516	0.0956	1.2128
O	2.2122	-0.0998	2.3661
O	3.7614	0.5973	0.8639
C	4.5994	0.9959	1.9596
H	4.1026	1.7900	2.5568
H	4.8210	0.1343	2.6263
H	5.5308	1.3817	1.5009
O	-2.2181	1.2713	0.6916
O	-1.3692	-0.8861	0.3740
C	-3.0515	0.6957	1.7001
H	-3.9388	0.2014	1.2372
H	-3.4223	1.5574	2.2940
C	-2.2666	-0.3147	2.5939
C	-1.0314	-0.7366	1.7583
H	-0.6491	-1.7279	2.0780

H	-0.2047	-0.0072	1.8980
C	-1.7855	0.3573	3.8940
H	-2.6452	0.6192	4.5520
H	-1.1110	-0.3158	4.4698
H	-1.2200	1.2898	3.6730
C	-3.1570	-1.5320	2.9050
H	-3.4024	-2.0899	1.9735
H	-2.6451	-2.2347	3.6007
H	-4.1149	-1.2236	3.3832
H	-3.3238	0.8914	-1.6179

6 References

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Abbreviations

br	broad (spectral)
n-BuLi	n-butyl lithium
calcd.	Calculated
°C	degrees Celcius
δ	chemical shift in parts per million downfield from tetramethylsilane
COSY	correlation spectroscopy
EI	electronic ionisation
Et	ethyl
g	gram(s)
HRMS	high resolution mass spectroscopy
IR	infrared spectroscopy
ISC	intersystem crossing
J	coupling constant
λ_{max}	wave length of maximum emission or absorption
Me	methyl
MHz	megahertz
mL	milliliter(s)
mmol	millimole(s)
Mp	melting point
NMR	nuclear magnetic resonance
ODPM	oxa-di-pi-methane
Ph	phenyl
ppm	parts per million (in NMR)
RT	room temperature
SAR	structure activity studies
THF	tetrahydrofurane
TLC	thin layer chromatograpy
TMS	trimethylsilyl

Curriculum Vitae

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